Q3D Elemental Impurities

This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

This document reached step 2B of the ICH Process on June 6, 2013.

For questions regarding this draft document, contact (CDER) John Leighton at 301-796-1398.

INTERNATIONAL CONFERENCE ON HARMONISATION OF TECHNICAL REQUIREMENTS FOR REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE

DRAFT CONSENSUS GUIDELINE

GUIDELINE FOR ELEMENTAL IMPURITIES

Q3D

Current *Step 2b* version

dated 26 July 2013

At Step 2 of the ICH Process, a consensus draft text or Guideline, agreed by the appropriate ICH Expert Working Group, is transmitted by the ICH Steering Committee to the regulatory authorities of the three ICH regions (the European Union, Japan and the USA) for internal and external consultation, according to national or regional procedures.

Q3D
Document History

Current *Step 2a* version

Code	History	Date
Q3D	Approval by the Steering Committee under *Step 2a*.	6 June 2013

Current *Step 2b* version

Code	History	Date
Q3D	Approval by the Steering Committee under *Step 2b* and release for public consultation.	6 June 2013
Q3D	Post sign-off corrigendum in: • Table 4.1 W and Al were removed from the list of included elemental impurities in Class 2B and 3 respectively. • Table A.2.1 the Class for Ni was changed to read 3 instead of 2.	14 June 2013
Q3D	Post sign-off minor editorial corrections including: removal of references to Appendix 5 (pgs i & 13); deletion of redundant text (pg 4); change of Option 2 to Option 2a (pg 10); insertion of omitted text under Safety Limiting Toxicity (pg 35); removal of duplicated redundant text (pg 41); replacing references to "metals" in text and "metal" in Table A.4.7 title with "elementals" and "elements" (pg 73); and deletion of header Table A.4.10 (pg 75).	26 July 2013
Q3D	Addition of line numbers to facilitate the provision of comments by stakeholders.	30 September 2013

GUIDELINE FOR ELEMENTAL IMPURITIES

Draft ICH Consensus Guideline
Released for Consultation on 26 July 2013, at *Step 2b* of the ICH Process

TABLE OF CONTENTS

GUIDELINE FOR ELEMENTAL IMPURITIES
Q3D

1. INTRODUCTION

Elemental impurities in drug products may arise from several sources; they may be added intentionally in synthesis, or may be present as contaminants (e.g., through interactions with processing equipment or by being present in components of the drug product) and are consequently detectable in the drug product. Since elemental impurities do not provide any therapeutic benefit to the patient, element impurity levels should be controlled within acceptable limits in the drug product. There are three components of this guideline: the evaluation of the toxicity data for potential elemental impurities, the establishment of a Permitted Daily Exposure (PDE) for each element of toxicological concern, and development of controls designed to limit the inclusion of elemental impurities in drug products to levels at or below the PDE. It is not expected that an applicant tightens the limits based on process capability provided that the elemental impurities in drug products are held at or below the PDE. The PDEs established in this guideline are considered to be protective of public health for all patient populations, including pediatric patients. In some cases, lower levels of elemental impurities may be needed when levels below toxicity thresholds have been shown to have an impact on other quality attributes of the drug product (e.g., element catalyzed degradation of drug substances). In addition, in the case of high PDEs, other limits may have to be considered from a pharmaceutical quality perspective; other guidelines should be consulted.

Developing a strategy to limit elemental impurities in the drug product is consistent with risk management processes identified in ICH Q9. The process is described in this guideline as a four step process to assess and control elemental impurities in the drug product: identify, analyse, evaluate, and control.

The PDE of the elements may change if new safety data become available. The guideline may be updated to include other elemental impurities or other routes of administration as new data become available. Any interested party can make a request and submit the relevant safety data to be considered.

2. SCOPE

The PDEs in this guideline have been established based on acceptable safety limits of potentially toxic elemental impurities. The guideline applies to new finished drug products (as defined in ICH Q6A and Q6B) and new drug products employing existing drug substances. The drug products containing: proteins and polypeptides (produced from recombinant or non-recombinant cell-culture expression systems), their derivatives, and products of which they are components (e.g., conjugates) are in the scope of this guideline. In addition, drug products containing synthetically produced polypeptides, polynucleotides, and oligosaccharides are within scope of this guideline.

This guideline does not apply to herbal products, radiopharmaceuticals, vaccines, cell metabolites, DNA products, allergenic extracts, cells, whole blood, cellular blood components, crude products of animal or plant origin, dialysate solutions not intended for systemic circulation or drug products containing elements that are intentionally included for therapeutic benefit.

46 This guideline does not apply to drug products used during clinical research stages of
47 development. In the later stages of development, the principles contained in this
48 guideline can be useful in evaluating elemental impurities that may be present in new
49 drug product prepared by the proposed commercial process.

50 The application of this guideline to existing marketed drug products will be addressed by
51 regional regulatory processes.

52 **3.   SAFETY ASSESSMENT OF POTENTIAL ELEMENTAL IMPURITIES**

53 **3.1   Principles of the Safety Assessment of Elemental Impurities for Oral,**
54 **Parenteral and Inhalation Routes of Administration**

55 The method used for establishing the PDE for each element impurity is discussed in
56 detail in Appendix 1. Elements evaluated in this guideline were assessed by reviewing
57 the publicly available data contained in scientific journals, government research reports
58 and studies, international regulatory standards (applicable to drug products) and
59 guidance, and regulatory authority research and assessment reports.   This process
60 follows the principles employed in ICH Q3C: Residual Solvents. The available
61 information was reviewed to establish the oral, parenteral and inhalation PDEs provided
62 in the guideline.

63 A summary safety assessment identifying the critical study for setting a PDE for each
64 element is included in Appendix 3. There are insufficient data to set PDEs by any route
65 of administration for osmium, rhodium, ruthenium and iridium. The PDEs for these
66 elements were established on the basis of their similarity to platinum. The PDEs for
67 each element included in the guideline are summarized in Appendix 2, Table A.2.1.

68 The factors considered in the safety assessment for establishing the PDE were:

69 • The oxidation state of the element likely to be present in the drug product;

70 • Human exposure and safety data when it provided applicable information;

71 • The most relevant animal study;

72 • Route of administration;

73 • Selection of the relevant endpoints or designations (e.g., International Agency for
74 Research on Cancer [IARC] classification, animal carcinogenicity, reproductive
75 toxicology, target organ toxicity, etc);

76 • The longest duration animal study was generally used to establish the PDE. In
77 some instances, a shorter duration animal study was considered the most
78 relevant study. The rationale for using the shorter duration study is provided in
79 the individual PDE assessment;

80 • In the absence of data and/or where data were available but were not considered
81 sufficient for a safety assessment for the parenteral and or inhalation route of
82 administration, default factors (see below) were used to derive the PDE from the
83 oral PDE;

84 • In inhalation drug products, soluble salts are more relevant than particulates to
85 assess elemental impurity toxicity. Therefore, inhalation studies using soluble
86 salts (when available) were preferred over studies using particulates for
87 inhalation assessment and derivation of inhalation PDEs.

88 In some cases, standards for daily intake for some of the elemental impurities discussed
89 in this guideline exist for food, water, air, and occupational exposure. These standards
90 have developed over time with different regional processes and may use different
91 modifying factors or other estimates (e.g., body weight for an individual). In some cases,
92 these standards are not only safety based, rather, based on practical considerations or

93   analytical capability. Where appropriate, these standards were considered in the
94   assessment and establishment of the PDEs using the approach as outlined in Appendix 1.

95   For PDEs established for inhalation (oral or parenteral routes as applicable), doses were
96   normalized to a 24 hour, 7 day exposure. If data were available for local toxicity to the
97   lung, those data were considered in establishing the inhalation PDE.

98   Where data were available but were not considered sufficient for a safety assessment for
99   the parenteral route of administration, modifying factors were employed as follows:

100   Oral bioavailability <1% divide by a modifying factor of 100
101   Oral bioavailability < 50% divide by a modifying factor of 10
102   Oral bioavailability between 50% and 90% divide by a modifying factor of 2
103   Oral bioavailability > 90% divide by a modifying factor of 1

104   Where inhalation and/or parenteral data were available but were not considered
105   sufficient for a safety assessment or Threshold Limit Value (TLV)/Time Weighted
106   Average (TWA) values were not available for the inhalation route of administration, a
107   calculated PDE was used based on the oral PDE divided by a modifying factor of 100
108   (Ball *et al.* 2007). In cases where the TLV/TWA or a nonclinical inhalation study was
109   used, the dose levels were normalized to a 24 hour, 7 day week.

110   PDEs for elements of low risk to human health as impurities in drug products were not
111   established. The elements in this category include: Fe, B, Al, W, Zn, K, Ca, Na, Mn, and
112   Mg.

113   For elements not included in this guideline for which there is limited or insufficient data,
114   the concepts used in this guideline can be used to determine appropriate PDEs.

115   **3.2   Other Routes of Administration**

116   PDEs were only established for oral, parenteral and inhalation routes of administration.
117   Sufficient data to permit the establishment of a PDE for other routes of administration
118   were generally unavailable. However, the concepts applied and described in this
119   guideline can be used to determine appropriate PDEs for other routes of administration.
120   Application of the parenteral PDE can provide the basis of a route-specific safety
121   assessment.

122   **3.3   Justification for Element Impurity Levels Higher than the PDE**

123   Levels of elemental impurities higher than the PDE may be acceptable in certain cases.
124   These cases could include, but are not limited to the following situations:

125   • less than daily dosing
126   • short term exposures (i.e., 30 days or less)
127   • specific indications (e.g., life-threatening, unmet medical needs, rare diseases)

128   Justification for increased levels in these situations should be made on a case by case
129   basis justifying the proposed level using a risk based approach. ICH Q3C and this
130   guideline use modifying factors for interspecies (Factor F1) and individual (Factor F2)
131   variability. These modifying factors serve as starting points in extrapolating available
132   data to obtain a PDE. The sub-factor approach (WHO, 2009), may be used to justify a
133   higher PDE, where data are available, using knowledge of the mode of action and
134   pharmacokinetic considerations. A justification may also include but is not limited to a
135   consideration of the duration of the study used to set the PDE relative to the intended
136   clinical use (Factor F3), the nature and severity of the toxicity observed, and whether the
137   toxicity was reversible (Factor F4).

138　An example of the sub-factor approach can be found elsewhere in a risk assessment for
139　boron (US Environmental Protection Agency [EPA], 2004).

140　**3.4　Parenteral Products**

141　The parenteral PDEs are applied irrespective of dose volume.

142　**4.　ELEMENT CLASSIFICATION**

143　The elemental impurities included in this guideline have been placed into categories that
144　are intended to facilitate decisions during the risk assessment.

145　　　• Class 1 elemental impurities, As, Cd, Hg, and Pb, are significantly toxic across all
146　　　　routes of administration. Typically they have limited or no use in the
147　　　　manufacture of pharmaceuticals but can be present as impurities in commonly
148　　　　used materials (e.g., mined excipients) and can not be readily removed from the
149　　　　material. Because of their unique nature, these four elemental impurities require
150　　　　consideration during the risk assessment across all potential sources of elemental
151　　　　impurities.

152　　　• Class 2 elemental impurities are toxic to a greater or lesser extent based on route
153　　　　of administration. In addition, some of the elements present in this category are
154　　　　infrequently observed as impurities in materials used to produce drug products
155　　　　and as such, unless intentionally added have a low probability of inclusion in the
156　　　　drug product and do not present a significant risk. Class 2 elemental impurities
157　　　　are further categorized to establish when they should be considered in the risk
158　　　　assessment and when their contribution can be judged to be negligible.

159　　　　　o Class 2A: The following elemental impurities require assessment across all
160　　　　　　potential sources and routes of administration: V, Mo, Se, and Co due to
161　　　　　　their higher relative natural abundance (US Geological Survey, 2005).

162　　　　　o Class 2B: The following elemental impurities require assessment across
163　　　　　　potential elemental impurity sources only if they are intentionally added
164　　　　　　to the processes used to generate the material under evaluation: Au, Tl,
165　　　　　　Pd, Pt, Ir, Os, Rh, Ag and Ru.

166　　　• Class 3 elemental impurities are impurities with relatively low toxicity (high
167　　　　PDEs) by the oral route administration but require consideration in the risk
168　　　　assessment for other routes of administration (e.g., inhalation and parenteral
169　　　　routes). For oral routes of administration, unless these elements are intentionally
170　　　　added as part of the process generating the material, they do not need to be
171　　　　considered during the risk assessment. For parenteral and inhalation products,
172　　　　the potential for inclusion of these elemental impurities should be evaluated
173　　　　during the risk assessment. The elemental impurities in this class include: Sb,
174　　　　Ba, Li, Cr, Cu, Sn, and Ni.

175　　　• Class 4 elemental impurities are elemental impurities that have been evaluated
176　　　　but for which a PDE has not been established due to their low inherent toxicity
177　　　　and/or regional regulations. If these elemental impurities are present or included
178　　　　in the drug product they are addressed following the practices defined by other
179　　　　guidelines and regional regulation. The elements in this class include: Al, B, Fe,
180　　　　Zn, K, Ca, Na, Mn, Mg, and W.

181　The classification system is summarized in Table 4.1.

182 **Table 4.1: Elemental Impurity Classification**
183

	Included Elemental Impurities	**Include in Risk Assessment?**
Class 1	As, Pb, Cd, Hg	Yes
Class 2A	V, Mo, Se, and Co	Yes
Class 2B	Ag, Au, Tl, Pd, Pt, Ir, Os, Rh, and Ru	Yes only if intentionally added
Class 3	Sb, Ba, Li, Cr, Cu, Sn, Ni	Dependent upon route of administration – see Class 3 description
Class 4	B, Fe, Zn, K, Ca, Na, Mn, Mg, W, Al	No

184 **5. ASSESSMENT AND CONTROL OF ELEMENTAL IMPURITIES**

185 In developing the control strategy for elemental impurities in drug products, the
186 principles of quality risk management, described in ICH Q9, should be considered. The
187 risk assessment should be based on scientific knowledge and principles. It should link
188 patient safety considerations with an understanding of the product and its
189 manufacturing process (ICH Q8 and Q11). In the case of elemental impurities, the
190 product risk assessment would therefore be focused on assessing the levels of elemental
191 impurities in a drug product in relation to the PDEs presented in this guidance.
192 Information for this assessment includes but is not limited to: data generated by the
193 applicant, information supplied by drug substance, reagent and/or excipient
194 manufacturers or data available in published literature.

195 The applicant should document the assessment and control approaches in an appropriate
196 manner. The level of effort and formality of the assessment should be proportional to the
197 level of risk. It is neither always appropriate nor always necessary to use a formal risk
198 management process (using recognized tools and/or formal procedures, e.g., standard
199 operating procedures.) The use of informal risk management processes (using empirical
200 tools and/or internal procedures) can also be considered acceptable. Tools to assist in the
201 risk assessment are described in ICH Q9 and will not be presented in this guideline.

202 **5.1 General Principles**

203 For the purposes of this guideline, the assessment process can be described in four steps:
204 identify, analyse, evaluate and control. In many cases, the steps are considered
205 simultaneously. For example, the analyse and evaluate steps may be iterative steps that
206 initiate adjustments to control elements. The outcome of the assessment may be the
207 result of iterations to develop a final approach to ensure the potential elemental
208 impurities do not exceed the PDE.

209 Identify: Identify known and potential sources of elemental impurities that may
210   find their way into the drug product.

211 Analyze: Determine the probability of observance of a particular elemental impurity
212   in the drug product.

5

213 Evaluate: Compare the observed or predicted levels of elemental impurities with the
214   established PDE.

215 Control: Document and implement a control strategy to limit elemental impurities
216   in the drug product.

217 **5.2 Potential Sources of Elemental Impurities**

218 In considering the production of a drug product, there are several broad categories of
219 potential sources of elemental impurities.

220 • Residual elemental impurities resulting from elements intentionally added to
221   reactions or processes leading up to the preparation of the drug substance,
222   reagents, starting materials or excipients (e.g., metal catalysts).

223 • Elemental impurities known or suspected of being present in the drug substance,
224   reagents, water, starting materials or excipients used in the preparation of the
225   drug product.

226 • Elemental impurities known or suspected of being introduced into the drug
227   substance and/or drug product from manufacturing equipment.

228 • Elemental impurities that are known or suspected of being leached into the drug
229   substance and drug product from container closure systems.

230 The following diagram shows an example of typical materials or components used in the
231 production of a drug product. Each of these materials or components may contribute
232 elemental impurities to the drug product, through any individual or any combination of
233 the potential sources listed above. During the assessment, the potential contributions
234 from each of these materials or components should be considered to determine the
235 overall contribution of elemental impurities to the drug product.
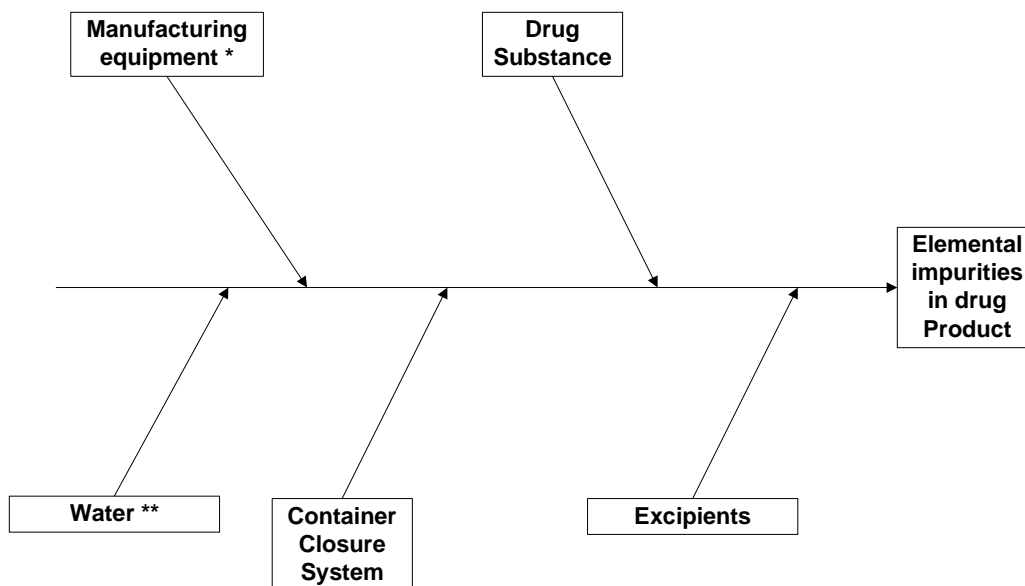
236
237

238 * The risk of inclusion of elemental impurities can be reduced through process
239 understanding, equipment selection, equipment qualification and Good Manufacturing
240 Practice (GMP) processes.

241 ** The risk of inclusion of elemental impurities from water can be reduced by complying
242 with compendial (e.g., European Pharmacopoeia, Japanese Pharmacopoeia, US

243 Pharmacopeial Convention) water quality requirements, if purified water or water for
244 injection is used in the process(es).

5.3   Assessment – Identification of Potential Elemental Impurities

246 **Class 1 elemental impurities:**   Due to their inherent toxicity, the risk assessment
247 should include an assessment of the Class 1 elemental impurities. All potential sources
248 of elemental impurities should be evaluated for the potential to transfer the Class 1
249 elemental impurities to the drug product.

250 **Potential elemental impurities derived from intentionally added catalysts or**
251 **reagents:** For this category, the identity of the potential impurities is known and
252 techniques for controlling the elemental impurities are easily characterized and defined.
253 The predominant elemental impurities that comprise this group are the Class 2 and 3
254 elemental impurities. Table 5.1 shows the suggested consideration in the risk
255 assessment for each of the elemental impurities covered in this guideline. As identified,
256 if any (Class 1, 2, or 3) elemental impurity is added, it should be considered in the risk
257 assessment.

258 **Potential elemental impurities with a relatively high abundance and/or are**
259 **impurities in excipients or reagents**: Elemental impurities known or suspected of
260 being present in the drug substance, reagents, starting materials or excipients used in
261 the preparation of the drug product should be considered. These elemental impurities
262 are often associated with mined materials and excipients. The presence of these
263 impurities can be variable, especially with respect to mined excipients, which can
264 complicate the risk assessment. The variation should be considered when establishing
265 the probability for inclusion in the drug product. The elemental impurities that are of
266 most significant to this potential source include the Class 1 and Class 2A elemental
267 impurities (see Table 4.1). For parenteral and inhalation routes of administration, the
268 risk assessment should evaluate the probability for inclusion of the Class 1 and most 3
269 elemental impurities as shown in Table 5.1.

270 **Potential elemental impurities derived from manufacturing equipment:** The
271 contribution of elemental impurities may be limited and the subset of elemental
272 impurities that should be considered in the risk assessment is relatively small and is
273 dependent on the equipment involved. Application of process knowledge, selection of
274 equipment, equipment qualification and GMP controls ensure a low contribution from
275 manufacturing equipment. The specific elemental impurities of concern should be
276 assessed based on knowledge of the composition of the components of the manufacturing
277 equipment. The assessment of this source of elemental impurities is one that can be
278 utilized potentially for many drug products using similar process trains and processes.

279 **Elemental impurities leached from container closure systems:** Identifying the
280 potential elemental impurities extracted from container closure systems should be based
281 on a scientific understanding of likely interactions between a particular drug product
282 type and its packaging. When a review of the materials of construction demonstrates
283 that the container closure system does not contain elemental impurities, no additional
284 assessment needs to be performed. It is recognized that the probability of elemental
285 leaching into solid dosage forms is minimal and does not require further consideration in
286 the assessment. For liquid and semi-solid dosage forms there is a higher probability that
287 elemental impurities could leach from the container closure system into the drug product
288 during the shelf-life of the product. Studies to understand potential extractables and
289 leachables from the final/actual container closure system (after washing sterilization,
290 irradiation) should be performed.

291 Factors that should be considered (for liquid and semi-solid dosage forms) include but are
292 not limited to:

293 • Hydrophilicity/hydrophobicity

294 • Ionic content

295 • pH

296 • Temperature (cold chain *vs* room temperature and processing conditions)

297 • Contact surface area

298 • Container/component composition

299 • Terminal sterilization

300 • Packaging process

301 • Component sterilization

302 • Migration potential

303 • Duration of storage

304 • Inclusion of metal chelating agents in the formulation (e.g., Ethylenediamine
305 Tetraacetic Acid [EDTA]).

306 **Table 5.1: Recommendation for Consideration During Risk Assessment**

Element	Class	If intentionally added (across all routes of administration)	If not intentionally added		
			Oral	Parenteral	Inhalation
As	1	yes	yes	yes	yes
Cd	1	yes	yes	yes	yes
Hg	1	yes	yes	yes	yes
Pb	1	yes	yes	yes	yes
Co	2A	yes	yes	yes	yes
Mo	2A	yes	yes	yes	yes
Se	2A	yes	yes	yes	yes
V	2A	yes	yes	yes	yes
Ag	2B	yes	no	no	no
Au	2B	yes	no	no	no
Ir	2B	yes	no	no	no
Os	2B	yes	no	no	no
Pd	2B	yes	no	no	no
Pt	2B	yes	no	no	no
Rh	2B	yes	no	no	no
Ru	2B	yes	no	no	no
Tl	2B	yes	no	no	no
Ba	3	yes	no	no	yes
Cr	3	yes	no	no	yes
Cu	3	yes	no	yes	yes
Li	3	yes	no	yes	yes
Ni	3	yes	no	yes	yes
Sb	3	yes	no	yes	yes
Sn	3	yes	no	yes	yes

307

308 **5.4   Assessment – Analysis and Evaluation**

309 As the potential elemental impurity identification process is concluded, there are several
310 possible outcomes: the process and product review does not identify any potential
311 elemental impurities or the process identifies a list of one or more potential elements.
312 When present, the elemental impurities may have a single source or multiple sources. In
313 addition, a number of elemental impurities will be excluded from consideration based on
314 the assessment of their probability of occurrence and their potential to exceed the PDE.
315 In order to accurately complete the assessment, data regarding potential elemental
316 impurity levels may be needed. The data for this assessment can come from a number of
317 sources that include, but are not limited to:

318 • Prior knowledge
319 • Published literature
320 • Data generated from similar processes
321 • Supplier information or data
322 • Analysis of the components of the drug product
323 • Analysis of the drug product

324 The applicant's risk assessment can be facilitated with information about the potential
325 elemental impurities provided by suppliers of drug substances, excipients, starting
326 materials, reagents, container closure systems, and manufacturing equipment.

327 Since the PDE is established on the drug product, it is necessary to compare the
328 predicted or known levels of the elemental impurities identified with the established
329 PDE in order to define the appropriate steps to take in developing an approach to control
330 potential elemental impurities in the drug product. This may be done in several different
331 ways and the applicant should consider which option is most appropriate for their use
332 given the elemental impurities identified in combination with the source of the elemental
333 impurity.

334 **5.5   Converting Between PDEs and Concentration Limits**

335 The PDEs, reported in micrograms per day (µg/day) provided in this document give the
336 maximum permitted quantity of each element that may be contained in the maximum
337 daily intake of a drug product.   Because the PDE reflects only total exposure from the
338 drug product, it is useful to convert the PDE, into concentrations as a tool in evaluating
339 elemental impurities in drug products or their components. The following options
340 describe some acceptable approaches to establishing concentrations of elemental
341 impurities in drug products or components that would assure that the drug product
342 meets the PDEs. The applicant may select any of these options as long as the resulting
343 permitted concentrations assure that the drug product meets the PDEs for elemental
344 impurities. In the choice of a specific option the applicant must have knowledge of, or
345 make assumptions about, the daily intake of the drug product. In all cases, the PDE
346 should be met. The permitted concentration limits may be used:

347 • As a tool in the risk assessment to compare the observed or predicted levels to the
348   PDE;
349 • In discussions with suppliers to help establish upstream controls that would
350   assure that the product meets the PDE;
351 • To establish concentration targets when developing in-process controls on
352   elemental impurities;
353 • To convey information regarding the controls on elemental impurities in
354   regulatory submissions.

355 As discussed in Section 5.2, there are multiple sources for elemental impurities in drug
356 products. When applying any of the options described below, elemental impurities from
357 container closure systems and manufacturing equipment should be taken into account
358 prior to calculating the maximum permitted concentration in the remaining components
359 (excipients and drug substance). If it is determined during the risk assessment that the
360 container closure systems and manufacturing equipment do not contribute to the
361 elemental impurity level in the drug product, they do not need to be considered.   Where
362 contributions from container closure systems and manufacturing equipment exist, these
363 contributions may be accounted for by subtracting the estimated daily intake from these
364 sources from the PDE prior to calculation of the allowed concentration in the excipients
365 and drug substance.

366 **Option 1: Common permitted concentration limits of elements across drug**
367 **product components for drug products with daily intakes of not more than 10**
368 **grams:**
369 This option is not intended to imply that all elements are present at the same
370 concentration, but rather provides a simplified approach to the calculations.

371 The option assumes the daily intake (amount) of the drug product is 10 grams or less,
372 and that elemental impurities identified in the risk assessment (the target elements) are
373 present in all components of the drug product. Using equation (1) below, and a daily
374 intake of 10 grams of drug product, this option calculates a common permissible target
375 elemental concentration for each component in the drug. This approach, for each target
376 element, allows determination of a fixed common maximum concentration in micrograms
377 per gram in each component. The calculated values are provided in Appendix 2 Table
378 A.2.2.

379

380
$$Concentration(\mu g/g) = \frac{PDE(\mu g/day)}{daily\ amount\ of\ drug\ product(g/day)} \qquad (1)$$

381

382 If all the components in a drug product meet the Option 1 concentrations for all target
383 elements identified in the risk assessment, then all these components may be used in
384 any proportion in the drug product. An example of this calculation is shown in Appendix
385 4 Table A.4.1. If the permitted concentrations in Appendix 2 Table A.2.2 are not applied,
386 Options 2a, 2b, or 3 must be followed.

387 **Option 2a: Common permitted concentration limits across drug product**
388 **components for a drug product with a specified daily intake**:
389 This option is similar to Option 1, except that the drug daily intake is not assumed to be
390 10 grams. The common permitted concentration of each element is determined using
391 Equation 1 and the actual maximum daily intake.

392 This approach, for each target element, allows determination of a fixed common
393 maximum concentration in micrograms per gram in each component based on the actual
394 daily intake provided. An example of this calculation is provided in Appendix 4 Table
395 A.4.2.

396 If all components in a drug product meet the Option 2a concentrations for all target
397 elements identified in the risk assessment, then all these components may be used in
398 any proportion in the drug product.

399 **Option 2b: Permitted concentration limits of elements across drug product**
400 **component materials for a product with a specified daily intake:**
401

402   This option requires additional information that the applicant may assemble regarding
403   the potential for specific elemental impurities to be present in specific drug product
404   components. The applicant may set permitted concentrations based on the distribution
405   of elements in the components (e.g., higher concentrations in components with the
406   presence of an element in question). For each element identified as potentially present
407   in the components of the drug product, the total mass of the elemental impurity in the
408   final drug product can be calculated as the sum of the product of the component material
409   masses at the maximum permitted concentrations established by the applicant. The
410   total mass of the elemental impurity in the drug product cannot exceed the PDEs given
411   in Appendix 2 Table A.2.1., as shown in equation 2. If the risk assessment has identified
412   that a specific element is not a potential impurity in a specific component, there is no
413   need to establish a quantitative result for that element in that component. This approach
414   allows that the maximum permitted concentration of an element in certain components
415   of the drug product may be higher than the Option 1 or Option 2a limit, but this should
416   then be compensated by lower allowable concentrations in the other components of the
417   drug product. Equation 2 may be used to set component-specific limits for each element
418   in each component of a drug product.

$$419 \qquad \mathrm{PDE}(\mu g/\mathrm{day}) \geq \sum_{k=1}^{N} C_k \cdot M_k \qquad\qquad (2)$$

420      $k =$ an index for each of N components in the drug product
421      $C_k =$ concentration of the elemental impurity in component k (µg/g)
422      $M_k =$ mass of component k in the maximum daily intake of the drug product (g)
423
424   An example of this calculation is provided in Appendix 4 Tables A.4.3 – A.4.5.

425   **Option 3: Finished Product Analysis:**

426   The concentration of each element may be measured in the final drug product. Equation
427   1 may be used with the maximum total daily dose of the drug product to calculate a
428   maximum permitted concentration of the elemental impurity. An example of this option
429   is provided in Appendix 4 Table A.4.6.

430   **5.6   Assessment Summary**

431   The process described above is intended to enable the applicant to focus on those
432   elements that require additional control elements. The process permits the applicant to
433   utilize information and knowledge gained across products to establish the particular
434   elemental impurities of concern in the specific drug product.

435   A number of factors can influence the level of the potential impurity in the drug product
436   and should also be considered in the assessment. These include but are not limited to:

437   •   Efficiency of removal of elemental impurities during further processing;

438   •   Natural abundance of elements (especially important for the categories of
439   elements which are not intentionally added);

440   •   Prior knowledge of elemental impurity concentration factors from specific
441   sources.

442   For elements that are added or are known to be potentially present in excipients or raw
443   materials, the analysis should consider the percentage of the excipient or raw material in
444   the drug product. Assessment of probable concentrations based on this percent of the
445   total composition of the drug product is an additional tool to determine if the
446   contribution is relevant. The analysis may include an assessment of the levels or
447   concentrations that are identified either in each component (including contributions from
448   the container closure system) or in the drug product.

449 The initial design of the facility and qualification of utilities and equipment, as part of
450 process qualification, would be expected to identify potential elemental impurities and
451 anticipated potential contributions to the drug product. In general, the contribution of
452 elemental impurities from manufacturing equipment and utilities is likely to be
453 negligible and would normally be addressed by implementing appropriate GMP
454 procedures. However, if the assessment demonstrated that the contribution was
455 significant, the anticipated levels of the identified elements should be reviewed as part of
456 the risk evaluation process.

457 Finally the applicant should consider the significance of the observed level relative to the
458 PDE of the element. As a measure of the significance of the observed elemental impurity
459 level, a control threshold is defined as a level that is 30% of the established PDE in the
460 drug product. This threshold is used to determine if additional controls may be required.
461 If the total elemental impurity level from all sources in the drug product is consistently
462 less than 30% of the PDE, applying appropriate assessment of the data and
463 demonstrating an adequate control strategy, then additional controls are not required.

464 If the assessment fails to demonstrate that an elemental impurity level is below the
465 control threshold, controls should be established to ensure that the elemental impurity
466 level does not exceed the PDE in the drug product.

467 In order to apply the control threshold, sources of variability should be understood.
468 Important factors include:

469 • Variability of the analytical method

470 • Variability of the elemental impurity level in the specific sources

471 • Variability of the elemental impurity level in the drug product

472 There are many acceptable approaches to document the assessment and may include:
473 tables, written summaries of considerations and conclusions of the assessment. The
474 summary should identify the elemental impurities, their sources, and the controls and
475 acceptance criteria as needed.

476 **5.7   Control of Elemental Impurities**

477 Control of elemental impurities includes decision making steps designed to reduce or
478 accept the presence of elemental impurities and their respective concentrations that
479 were identified and evaluated through the assessment process. When the assessment
480 determines that the levels of elemental impurities are below the control threshold, no
481 further control is required but periodic verification testing may be used to confirm that
482 the expected levels are consistent and predictive of future (see Section 5.8). The applicant
483 should provide a justification for the application of periodic verification testing.

484 When the control threshold is exceeded, the controls established should ensure that the
485 PDE is not exceeded. There are a number of control elements or approaches that an
486 applicant can pursue to control the elemental impurities in drug products. These include
487 but are not limited to:

488 • Identification of the steps in the manufacturing process that result in the
489 reduction of elemental impurities through specific or non-specific purification
490 steps;

491 • Implementation of in-process or upstream controls, designed to limit the
492 concentration of the elemental impurity in the drug product;

493 • Establishment of material (e.g., synthetic intermediates and raw materials) or
494 excipient specifications to limit the level of elemental impurity contributions
495 from those sources;

496   •   Establishment of specification limits for the drug substance;

497   •   Establishment of specification limits for the drug product;

498   •   Reliance on the compliance with compendial standards for materials used in
499   drug product processes;

500   •   Selection of appropriate container closure systems.

501 Where testing and acceptance criteria are established, periodic verification testing may
502 be appropriate in some cases (see Section 5.8).

503 An illustration of the risk assessment process described above can be found in Appendix
504 4.

5.8   Periodic Verification Testing

506 In situations where a test is recommended to be included in the specification to provide
507 suitable control of elemental impurities, but where routine measurement for release of
508 every batch may not be necessary, it may be possible to apply periodic verification testing
509 (periodic or skip lot testing as described in ICH Q6A). It should be noted that allowance
510 of periodic verification testing is considered to be helpful to provide periodic confirmation
511 that the controls contained within a process perform consistently over the lifecycle of the
512 product. Periodic testing is a means to ensure that the risk assessment assumptions are
513 valid and ensure that unintended or unknown process or material attributes have not
514 changed over time. Application of periodic verification testing should be applied to
515 processes or materials that are under a state of control (i.e., consistently meets
516 specifications and conforms to an appropriately established facility, equipment,
517 processing, and operational control regimen). If upon testing, the elemental impurity
518 level exceeds the PDE, the applicant should investigate the cause of the failure, reassess
519 the controls that are in place and determine if additional controls may be required.
520 Failures observed in periodic verification testing should be reported to the appropriate
521 regulatory authorities following the established procedures.

5.9   Special Considerations for Biotechnologically-Derived Products

523 For biotechnology-derived products, the risks associated with elemental impurities being
524 present at levels of safety concerns at the drug substance stage are considered low. This
525 is largely due to the following factors: a) elements are not typically used as catalysts or
526 reagents in the manufacturing of biotech products; b) elements are added at trace levels
527 in media feeds during cell culture processes, without accumulation and with significant
528 dilution/removal during further processing; c) typical purification schemes used in
529 biotech manufacturing such as chromatography steps and dialysis or Ultrafiltration-
530 Diafiltration (UF/DF) have the capacity to clear elements introduced in cell
531 culture/fermentation steps or from contact with manufacturing equipment to negligible
532 levels. As such, a specific control strategy that relates to the control of elements up to the
533 biotech drug substance is not generally needed. In cases where the biotechnology derived
534 drug substance contains synthetic elements (such as antibody-drug conjugates),
535 appropriate controls on the small molecule element for elemental impurities should be
536 performed.

537 However, potential elemental impurity sources included in drug product manufacturing
538 (e.g., excipients) and other environmental sources should be considered for
539 biotechnologically derived drug products. The contribution of these sources to the
540 finished product should be assessed as typically they are introduced in the drug product
541 manufacture at a step in the process where subsequent elemental impurity removal is
542 not generally performed. Risk factors that should be considered in this assessment
543 should include the type of excipients used, the processing conditions and their

544 susceptibility to contamination by environmental factors (e.g., controlled areas for sterile
545 manufacturing and use of purified water), as well as the overall dosing frequency.

546 **6. SPECIATION**

547 Speciation is defined as the separation of elemental impurities based on oxidation state,
548 organic combination or complexation state. The PDE has been established using the
549 toxicity information on the species expected to be in the drug product.

550 The applicant is not expected to provide speciation information; however, such
551 information could be used to justify higher levels for the more relevant or less toxic
552 species.

553 **7. ANALYTICAL PROCEDURES**

554 The determination of elemental impurities should be conducted using appropriate
555 procedures suitable for their intended purposes. Unless otherwise justified, the test
556 should be specific for each elemental impurity identified for control during the risk
557 assessment. Pharmacopoeial procedures or suitable validated alternative procedures for
558 determining levels of elemental impurities should be used.

559 **8. LIFE-CYCLE MANAGEMENT OF THE CONTROL STRATEGY FOR ELEMENTAL**
560 **IMPURITIES**

561 The quality system elements and management responsibilities described in ICH Q10 are
562 intended to encourage the use of science-based and risk-based approaches at each
563 lifecycle stage, thereby promoting continual improvement across the entire product
564 lifecycle. Product and process knowledge should be managed from development through
565 the commercial life of the product up to and including product discontinuation.

566 The effectiveness of the control strategy should be periodically evaluated throughout the
567 product lifecycle. Knowledge gained from development combined with commercial
568 manufacturing experience and data can be used to further improve process
569 understanding and process performance which can be used to make improvements to the
570 control strategy. It is recognized that the elemental impurity data available for some
571 components is somewhat limited at this time which may direct the applicant to a specific
572 series of control elements. Additional data, if developed, may lead to modifications of the
573 control strategy.

574 If changes to the drug product process(es) have the potential to change the elemental
575 impurity content of the drug product, the established control elements for elemental
576 impurities should be re-evaluated. Such changes could include but are not limited to:
577 changes in synthetic route, excipient supplier, raw materials, processes, equipment, or
578 facilities. All changes are subject to internal change management process (ICH Q10) and
579 if needed appropriate regional regulatory requirements.

580 **9. RECOMMENDATIONS FOR SUBMISSION OF ELEMENTAL IMPURITIES CONTROL**
581 **STRATEGY**

582 The information on the control strategy that is provided in a regulatory submission
583 should include the outcome of the risk assessment and a description of the controls
584 established to limit elemental impurities. A good location for the description of the
585 control strategy is Section 3.2.P.5.6. This summary should include appropriate references
586 to the locations of controls on elemental impurities defined in the control strategy (e.g.,
587 3.2.S and 3.2.P). A summary of the approach used to develop the control strategy may be
588 included in the Quality Overall Summary.

589 **REFERENCES**

590 Ball D, Blanchard J, Jacobson-Kram D, McClellan R, McGovern T, Norwood DL et al.
591 Development of safety qualification thresholds and their use in orally inhaled and nasal
592 drug product evaluation. Toxicol Sci 2007;97(2):226-36.

593 Haxel GB, Hedrick JB, Orris GJ. Rare earth elements-critical resources for high
594 technology. US Geological Survey 2005;Fact Sheet 087-02.

595 IPCS. Principles and methods for the risk assessment of chemicals in food, chapter 5:
596 dose-response assessment and derivation of health based guidance values.
597 Environmental Health Criteria 240. International Programme on Chemical Safety.
598 World Health Organization, Geneva. 2004; Table 5.5.

599 US EPA. 0410 Boron and Compounds. Integrated Risk Management System (IRIS).
600 2004.

601 GLOSSARY

602 **ATSDR**:

603 Agency for Toxic Substances and Disease Registry.

604 **CEC:**

605 Commission of the European Community.

606 **CFR**:

607 Code of Federal Regulations (USA).

608 **Change Management:**

609 A systematic approach to proposing, evaluating, approving, implementing and reviewing
610 changes. (ICH Q10)

611 **Container Closure System:**

612 The sum of packaging components that together contain and protect the dosage form.
613 This includes primary packaging components and secondary packaging components, if
614 the latter are intended to provide additional protection to the drug product. A packaging
615 system is equivalent to a container closure system. (ICH Q1A)

616 **Control Strategy:**

617 A planned set of controls, derived from current product and process understanding,
618 which assures process performance and product quality. The controls can include
619 parameters and attributes related to drug substance and drug product materials and
620 components, facility and equipment operating conditions, in-process controls, finished
621 product specifications, and the associated methods and frequency of monitoring and
622 control. (ICH Q10)

623 **Control Threshold:**

624 A limit that is applied during the assessment of elemental impurities to determine if
625 additional control elements may be required to ensure that the PDE is not exceeded in
626 the drug product. The limit is defined as 30% of the PDE of the specific elemental
627 impurity under consideration.

628 **Daily Dose**:

629 The total mass of drug product that is consumed by a patient on a daily basis.

630 **EFSA:**

631 European Food Safety Agency.

632 **EHC:**

633 Environmental Health Criteria. (WHO)

634 **EU SCOEL:**

635 European Scientific Committee on Occupational Exposure Limits.

636 **IARC**:

637 International Agency for Research on Cancer.

638 **Inhalation Unit Risk**:

639 The upper-bound excess lifetime cancer risk estimated to result from continuous
640 exposure to an agent at a concentration of 1 µg/L in water, or 1 µg/m³ in air. The
641 interpretation of inhalation unit risk would be as follows: if unit risk = 2 x 10-6 per µg/L,
642 2 excess cancer cases (upper bound estimate) are expected to develop per 1,000,000

643 people if exposed daily for a lifetime to 1 µg of the chemical in 1 liter of drinking water.
644 (US EPA)

645 **IPCS:**

646 International Programme for Chemical Safety.

647 **IUPAC:**

648 International Union of Pure and Applied Chemistry.

649 **IRIS**:

650 Integrated Risk Identification System, United States Environmental Protection Agency.

651 **Lowest-Observed-Adverse-Effect Level (LOAEL):**

652 Lowest concentration or amount of a substance *(dose)*, found by experiment or
653 observation, which causes an adverse effect on morphology, functional capacity, growth,
654 development, or life span of a target organism distinguishable from normal (control)
655 organisms of the same species and strain under defined conditions of exposure. (IUPAC)

656 **Limit of Detection (LOD)**:

657 The limit of detection of an individual analytical procedure is the lowest amount of
658 analyte in a sample which can be detected but not necessarily quantitated as an exact
659 value. (ICH Q2)

660 **Lowest-Observed-Effect Level (LOEL):**

661 The lowest dose of substance in a study or group of studies that produces biologically
662 significant increases in frequency or severity of any effects in the exposed humans or
663 animals.

664 **Modifying Factor:**

665 A factor determined by professional judgment of a toxicologist and applied to bioassay
666 data to relate that data to human safety. (Q3C) (See related term Safety Factor)

667 **MRL**:

668 Minimal Risk Level.

669 **No-Observed-Adverse-Effect Level (NOAEL):**

670 Greatest concentration or amount of a substance, found by experiment or observation,
671 which causes no detectable adverse alteration of morphology, functional capacity, growth,
672 development, or life span of the target organism under defined conditions of exposure.

673 **No-Observed-Effect Level (NOEL):**

674 The highest dose of substance at which there are no biologically significant increases in
675 frequency or severity of any effects in the exposed humans or animals.

676 **NTP**:

677 National Toxicology Program.

678 **OELV**:

679 Occupational Exposure Limit Value.

680 **OSHA:**

681 Occupational Safety and Health Administration (USA).

682 **PEL:**

683 Permitted Exposure Limit.

684 **Permitted Daily Exposure:**

685 The maximum acceptable intake of elemental impurity in pharmaceutical products per
686 day.

687 **Product Lifecycle**:

688 All phases in the life of the product from the initial development through marketing
689 until the product's discontinuation. (ICH Q9)

690 **Quality**:

691 The degree to which a set of inherent properties of a product, system, or process fulfills
692 requirements (see ICH Q6A definition specifically for *quality* of drug substance and drug
693 products). (ICH Q9)

694 **Quality Risk Management**:

695 A systematic process for the assessment, control, communication, and review of risks to
696 the quality of the drug product across the product lifecycle. (ICH Q9)

697 **Quality System**:

698 The sum of all aspects of a system that implements quality policy and ensures that
699 quality objectives are met. (ICH Q10)

700 **Raw Material:**

701 A general term used to denote starting materials, reagents, and solvents intended for use
702 in the production of intermediates or Active Pharmaceutical Ingredients (APIs). (ICH
703 Q7)

704 **Risk**:

705 The combination of the probability of occurrence of harm and the severity of that harm.
706 (ISO/IEC Guide 51, ICH Q9)

707 **Risk Acceptance:**

708 The decision to accept risk. (ISO Guide 73)

709 **Risk Analysis**:

710 The estimation of the risk associated with the identified hazards. (ICH Q9)

711 **Risk Assessment**:

712 A systematic process of organizing information to support a risk decision to be made
713 within a risk management process. It consists of the identification of hazards and the
714 analysis and evaluation of risks associated with exposure to those hazards. (ICH Q9)

715 **Risk Control:**

716 Actions implementing risk management decisions. (ISO Guide 73)

717 **Risk Identification:**

718 The systematic use of information to identify potential sources of harm (hazards)
719 referring to the risk question or problem description. (ICH Q9)

720 **Risk Management**:

721 The systematic application of quality management policies, procedures, and practices to
722 the tasks of assessing, controlling, communicating, and reviewing risk. (ICH Q9)

723

724

725 **Safety:**

726 Practical certainty that adverse effects will not result from exposure to an agent under
727 defined circumstances. (EHC 240)

728 **Safety Assessment:**

729 An approach that focuses on the scientific understanding and measurement of chemical
730 hazards as well as chemical exposures, and ultimately the risks associated with them.
731 Often (and in this guideline) used synonymously with risk assessment. *Related term*:
732 Risk assessment. (EHC 340)

733 **Safety Factor:**

734 A composite (reductive) factor applied by the risk assessment experts to the No-
735 Observed-Adverse-Effect Level (NOAEL) or other reference point, such as the
736 benchmark dose or benchmark dose lower confidence limit, to derive a reference dose
737 that is considered safe or without appreciable risk, such as an acceptable daily intake or
738 tolerable daily intake (the NOAEL or other reference point is divided by the safety factor
739 to calculate the reference dose). The value of the safety factor depends on the nature of
740 the toxic effect, the size and type of population to be protected, and the quality of the
741 toxicological information available. Related terms: Assessment factor, Uncertainty factor.
742 (EHC 240)

743 **Severity**:

744 A measure of the possible consequences of a hazard. (ICH Q9)

745 **Starting Material**:

746 A material used in the synthesis of a new drug substance that is incorporated as an
747 element into the structure of an intermediate and/or of the new drug substance. Starting
748 materials are normally commercially available and of defined chemical and physical
749 properties and structure. (ICH Q3A)

750 **Threshold Limit Value (TLV):**

751 The concentration in air to which it is believed that most workers can be exposed daily
752 without an adverse effect (i.e., effectively, the threshold between safe and dangerous
753 concentrations). The values were established (and are revised annually) by the ACGIH
754 and are time-weighted concentrations (TWA) for a 7- or 8-hour workday and 40-hour
755 workweek, and thus are related to chronic effects. (IUPAC)

756 **Time Weighted Average (TWA):**

757 As defined by ACGIH, time-weighted average concentration for a conventional 8-hour
758 workday and a 40-hour workweek. (IUPAC)

759 **URF**:

760 Unit Risk Factor.

761 **US DoL:**

762 United States Department of Labor.

763 **US EPA**:

764 United States Environmental Protection Agency.

765 **WHO**:

766 World Health Organization.

767 **Appendix 1: Method for Establishing Exposure Limits**

768 The Gaylor-Kodell method of risk assessment (Gaylor DW, Kodell RL. Linear
769 Interpolation algorithm for low dose assessment of toxic substance. J Environ Pathol
770 Toxicol 1980;4:305) is appropriate for carcinogenic elemental impurities. Only in cases
771 where reliable carcinogenicity data are available should extrapolation by the use of
772 mathematical models be applied to setting exposure limits. Exposure limits for
773 carcinogenic elemental impurities could be determined with the use of a large safety
774 factor (i.e., 10,000 to 100,000) with respect to the No-Observed-Effect Level (NOEL).

775 Acceptable exposure levels for elemental impurities in this guideline were established by
776 calculation of PDE values according to the procedures for setting exposure limits in
777 pharmaceuticals (Pharmacopeial Forum, Nov-Dec 1989), and the method adopted by
778 IPCS for Assessing Human Health Risk of Chemicals (Environmental Health Criteria
779 [EHC] 170, WHO, 1994). These methods are similar to those used by the US EPA (IRIS)
780 and the US FDA (Red Book) and others. The method is outlined here to give a better
781 understanding of the origin of the PDE values. It is not necessary to perform these
782 calculations in order to use the PDE values tabulated in Appendix 2 of this document.

783 PDE is derived from the NOEL, or the Lowest-Observed-Effect Level (LOEL) in the most
784 relevant animal study as follows:

785 PDE = NOEL x Mass Adjustment/[F1 x F2 x F3 x F4 x F5] *(1)*

786 The PDE is derived preferably from a NOEL. If no NOEL is obtained, the LOEL may be
787 used. Modifying factors proposed here, for relating the data to humans, are the same
788 kind of "uncertainty factors" used in Environmental Health Criteria (EHC 170, World
789 Health Organization [WHO], Geneva, 1994), and "modifying factors" or "safety factors" in
790 Pharmacopeial Forum. The assumption of 100% systemic exposure is used in all
791 calculations regardless of route of administration.

792 The modifying factors are as follows:

793 F1 = A factor to account for extrapolation between species

794 F1 = 5 for extrapolation from rats to humans

795 F1 = 12 for extrapolation from mice to humans

796 F1 = 2 for extrapolation from dogs to humans

797 F1 = 2.5 for extrapolation from rabbits to humans

798 F1 = 3 for extrapolation from monkeys to humans

799 F1 = 10 for extrapolation from other animals to humans

800 F1 takes into account the comparative surface area: body mass ratios for the species
801 concerned and for man. Surface area (S) is calculated as:

802 $S = kM^{0.67}$ (2)

803 in which M = body mass, and the constant k has been taken to be 10. The body masses
804 used in the equation are those shown below in Table A.1.1

805 F2 = A factor of 10 to account for variability between individuals

806 A factor of 10 is generally given for all elemental impurities, and 10 is used consistently
807 in this guideline

808 F3 = A variable factor to account for toxicity studies of short-term exposure

809 F3 = 1 for studies that last at least one half lifetime (1 year for rodents or rabbits; 7
810 years for cats, dogs and monkeys)

811   F3 = 1 for reproductive studies in which the whole period of organogenesis is covered

812   F3 = 2 for a 6-month study in rodents, or a 3.5-year study in non-rodents

813   F3 = 5 for a 3-month study in rodents, or a 2-year study in non-rodents

814   F3 = 10 for studies of a shorter duration

815   In all cases, the higher factor has been used for study durations between the time points,
816   e.g., a factor of 2 for a 9-month rodent study.

817   F4 = A factor that may be applied in cases of severe toxicity, e.g., non-genotoxic
818   carcinogenicity, neurotoxicity or teratogenicity. In studies of reproductive toxicity, the
819   following factors are used:

820   F4 = 1 for fetal toxicity associated with maternal toxicity

821   F4 = 5 for fetal toxicity without maternal toxicity

822   F4 = 5 for a teratogenic effect with maternal toxicity

823   F4 = 10 for a teratogenic effect without maternal toxicity

824   F5 = A variable factor that may be applied if the no-effect level was not established

825   When only an LOEL is available, a factor of up to 10 could be used depending on the
826   severity of the toxicity.

827   The mass adjustment assumes an arbitrary adult human body mass for either sex of 50
828   kg. This relatively low mass provides an additional safety factor against the standard
829   masses of 60 kg or 70 kg that are often used in this type of calculation. It is recognized
830   that some adult patients weigh less than 50 kg; these patients are considered to be
831   accommodated by the built-in safety factors used to determine a PDE.

832   As an example of the application of this equation, consider a toxicity study of cobalt in
833   human volunteers is summarized in Agency for Toxic Substances and Disease Registry
834   (ATSDR, 2004, op/. cit., Davis JE and Fields JP. Proc Soc Exp Biol Med 1958;99:493-5).
835   The Lowest-Observed-Adverse-Effect Level (LOAEL) for polycythemia is 1 mg/kg/day.
836   The PDE for cobalt in this study is calculated as follows:

837   PDE = 1 mg/kg/day x 50 kg/[1 x 10 x 10 x 1 x 10] = 0.05 mg/day = 50 μg/day

838   In this example,

839   F1 = 1 study in humans

840   F2 = 10 to account for differences between individual humans

841   F3 = 10 because the duration of the study was only 3 weeks

842   F4 = 1 because no severe toxicity was encountered

843   F5 = 10 because a LOAEL was used

844

Table A.1.1: Values Used in the Calculations in this Document

Rat body weight	425 g	Mouse respiratory volume	43 L/day
Pregnant rat body weight	330 g	Rabbit respiratory volume	1440 L/day
Mouse body weight	28 g	Guinea pig respiratory volume	430 L/day
Pregnant mouse body weight	30 g	Human respiratory volume	28,800 L/day
Guinea pig body weight	500 g	Dog respiratory volume	9,000 L/day
Rhesus monkey body weight	2.5 kg	Monkey respiratory volume	1,150 L/day
Rabbit body weight (pregnant or not)	4 kg	Mouse water consumption	5 mL/day
Beagle dog body weight	11.5 kg	Rat water consumption	30 mL/day
Rat respiratory volume	290 L/day	Rat food consumption	30 g/day

846 **Appendix 2: Established PDEs for Elemental Impurities**

847 **Table A.2.1: Permitted Daily Exposures for Elemental Impurities[1]**

Element	Class[2]	Oral PDE µg/day	Parenteral PDE, µg/day	Inhalation PDE, µg/day
As	1	15	15	1.9
Cd	1	5.0	6.0	3.4
Hg	1	40	4.0	1.2
Pb	1	5.0	5.0	5.0
Co	2A	50	5.0	2.9
Mo	2A	180	180	7.6
Se	2A	170	85	140
V	2A	120	12	1.2
Ag	2B	170	35	6.9
Au	2B	130	130	1.3
Ir[3]	2B	1000	10	1.4
Os[3]	2B	1000	10	1.4
Pd	2B	100	10	1.0
Pt	2B	1000	10	1.4
Rh[3]	2B	1000	10	1.4
Ru[3]	2B	1000	10	1.4
Tl	2B	8.0	8.0	69
Ba	3	13000	1300	340
Cr	3	11000	1100	2.9
Cu	3	1300	130	13
Li	3	780	390	25
Ni	3	600	60	6.0
Sb	3	1200	600	22
Sn	3	6400	640	64

848 [1] PDEs reported in this table are rounded to 2 significant figures (µg/day).
849 [2] Classification as defined in Section 4.
850 [3] Insufficient data to establish an appropriate PDE; the PDE was established based on
851   platinum PDE.
852

853 **Table A.2.2: Permitted Concentrations of Elemental Impurities for Option 1**

854 The values presented in this table represent permitted concentrations in micrograms per
855 gram for elemental impurities in drug products, drug substances and excipients. These
856 concentration limits are intended to be used when Option 1 is selected to assess the
857 elemental impurity content in drug products with daily doses of not more than 10 grams
858 per day. The numbers in this table are based on Table A.2.1.

Element	Class	Oral Concentration µg/g	Parenteral Concentration µg/g	Inhalation Concentration µg/g
As	1	1.5	1.5	0.29
Cd	1	0.50	0.60	0.34
Hg	1	4.0	0.40	0.12
Pb	1	0.50	0.50	0.50
Co	2A	5.0	0.50	0.29

Mo	2A	18	18	0.76
Se	2A	17	8.5	14
V	2A	12	1.2	0.12
Ag	2B	17	3.5	0.69
Au	2B	13	13	0.13
Ir**	2B	100	1.0	0.14
Os**	2B	100	1.0	0.14
Pd	2B	10	1.0	0.10
Pt	2B	100	1.0	0.14
Rh**	2B	100	1.0	0.14
Ru**	2B	100	1.0	0.14
Tl	2B	0.80	0.80	6.9
Ba	3	1300	130	34
Cr	3	1100	110	0.29
Cu	3	130	13	1.3
Li	3	78	39	2.5
Ni	3	60	6.0	0.60
Sb	3	120	60	2.2
Sn	3	640	64	6.4

859

860 ** Insufficient data to establish an appropriate PDE; the PDE was established based on
861   platinum PDE

862 **Appendix 3: Individual Safety Assessments**

863 **ANTIMONY**

864 **Summary of PDE for Antimony**

Antimony (Sb)			
	Oral	Parenteral	Inhalation
PDE (µg/day)	1200	600	22

865 **Introduction**

866 Antimony (Sb) is a silvery white naturally occurring metalloid element that is used in
867 various manufacturing processes. Small amounts of Sb are found in the earth's crust. It
868 exists in valence states of 3 and 5. Metallic Sb and a few trivalent Sb compounds are the
869 most significant regarding exposure potential and toxicity. Some antimonials, such as Sb
870 potassium tartrate, have been used medicinally as parasiticides. Antimony trioxide is
871 being used as a catalyst (e.g., in the manufacturing of PolyEthylene Terephthalate [PET]
872 used for container closure system components). Antimony is nutritionally not essential
873 and no metabolic function is known (ATSDR, 1992).

874 **Safety Limiting Toxicity**

875 Because of the limited *in vitro* genotoxicity data and the lack of *in vivo* tests, the
876 genotoxicity of Sb cannot be determined (ATSDR, 1992). In humans and animals, the
877 gastrointestinal tract (irritation, diarrhea, vomiting) appears to be the primary target
878 organ after oral exposure. In subchronic studies in rats lower mean body weights and
879 adverse liver findings were the most sensitive endpoints. Inhalation of high levels of Sb
880 over a long period can cause adverse respiratory effects in both humans and animals.

881 **PDE – Oral Exposure**

882 Limited oral data on Sb exposure is available in mice and rats (Schroeder *et al.* 1968;
883 Schroeder *et al.* 1970; Poon *et al.* 1998). The WHO evaluated Sb in drinking water (WHO,
884 2003). Lynch *et al.* concluded that a NOAEL from a 90 day drinking water rat study
885 using antimony potassium tartrate was 6 mg/kg/day based on lower mean body weight
886 and reduced food consumption (Lynch, 1999). This finding is consistent with the earlier
887 reports from Schroeder *et al*. Thus, the Permitted Daily Exposure (PDE) for oral
888 exposure was determined on the basis of the lowest NOAEL, i.e., 50 mg/L (equivalent to
889 6.0 mg Sb/kg/day).

890 Taking into account the modifying factors (F1-F5 as discussed in Appendix 1), the oral
891 PDE is calculated as below:

892 PDE = 6000 µg/kg/day x 50 kg / 5 x 10 x 5 x 1 x 1 = 1200 µg/day.

893 **PDE – Parenteral Exposure**

894 Adverse liver findings were the most sensitive endpoint in rats after repeated
895 intraperitoneal administration. Thus, the PDE for intraperitoneal exposure was
896 determined on the basis of the lowest NOAEL, i.e., 3.0 mg Sb/kg/day. This value was
897 obtained from a 90-day study in rats (based on adverse liver findings at 6 mg/kg in male
898 rats exposed to Sb potassium tartrate *via* intraperitoneal injection) (NTP, 1992).

899 Taking into account the modifying factors (F1-F5 as discussed in Appendix 1), the
900 human intraperitoneal PDE is calculated as below:

25

901   PDE = 3000 µg/kg/day x 50 kg / 5 x 10 x 5 x 1 x 1 = 600 µg/day.

902   **PDE – Inhalation Exposure**

903   Sub chronic and chronic inhalation rat studies have been conducted. The lung effects
904   observed across these studies were consistent. Using the data from a 13 week inhalation
905   rat study using antimony trioxide dust, (Newton *et al.* 1994), a NOAEL of 1.08 mg/m^3
906   was used to determine the inhalation PDE (~83% Sb). At higher dose levels an increase
907   in mean absolute and relative lung weights were observed, a finding not seen in the one
908   year oncogenicity study.

909   Taking into account the modifying factors (F1-F5 as discussed in Appendix 1), the
910   inhalation PDE is calculated as:

911   For continuous dosing = $\dfrac{0.9 \text{ mg/m}^3 \text{ x 6 h x 5 d}}{24 \text{ h x 7 d}}$ = $\dfrac{0.16 \text{ mg/m}^3}{1000 \text{ L/m}^3}$ = 0.00016 mg/L
912
913

914   Daily dose = $\dfrac{0.00016 \text{ mg/L x 290 L/d}}{.425 \text{ kg bw}}$ = 0.11 mg/kg/d
915
916

917   PDE = 0.11 mg/kg/d x 50 kg / 5 x 10 x 5 x 1 x 1 = 22 µg/d.
918

919   **REFERENCES**

920   ATSDR. Toxicological profile for antimony and compounds. Agency for Toxic Substances
921   and Disease Registry, Public Health Service, U.S. Department of Health and Human
922   Services, Atlanta, GA. 1992.

923   Lynch BS, Capen CC, Nestmann ER, Veenstra G, Deyo JA. Review of subchronic/chronic
924   toxicity of antimony potassium tartrate. Reg Toxicol Pharmacol 1999;30(1):9-17.

925   Newton PE, Bolte HF, Daly IW, Pillsbury BD, Terrill JB, Drew RT, et al. Subchronic
926   and chronic inhalation toxicity of antimony trioxide in the rat. Fundam Appl Toxicol
927   1994;22:561-76.

928   NTP. Technical report on toxicity studies of antimony potassium tartrate in F344/N rats
929   and B6C3F1 mice (drinking water and intraperitoneal injection studies). National
930   Toxicology Program, Public Health Service, U.S. Department of Health and Human
931   Services, Research Triangle Park, NC. 1992; NTP Toxicity Report Series No. 11.

932   Poon R, Chu I, Lecavalier P, Valli VE, Foster W, Gupta S, et al. Effects of antimony on
933   rats following 90-day exposure via drinking water. Food Chem Toxicol 1998;36:20–35.

934   Schroeder HA, Mitchner M, Nasor AP, Balassa JJ, Kanisawa M. Zirconium, niobium,
935   antimony and fluorine in mice: effects on growth, survival and tissue levels. J Nutr
936   1968;95:95-101.

937   Schroeder HA, Mitchner M, Nasor AP. Zirconium, niobium, antimony, vanadium and
938   lead in rats: life term studies. J. Nutr 1970;100(1):59-68.

939   WHO. Antimony in drinking-water. Background document for development of WHO
940   guidelines for drinking-water quality. World Health Organization, Geneva. 2003.

941   **ARSENIC**

942   **Summary of PDE for Arsenic**

Arsenic (As)			
	Oral	Parenteral	Inhalation
PDE (µg/day)	15	15	1.9

943

944   **Introduction**

945   Arsenic (As) is ubiquitous in the environment and present in food, soil, drinking water
946   and in air. Inorganic As occurs in trivalent (e.g., arsenic trioxide, sodium arsenite) or
947   pentavalent forms (e.g., sodium arsenate, arsenic pentoxide, arsenic acid). Arsenic has no
948   known useful biological function in human or mammalian organisms. This assessment
949   focuses on inorganic As, since this is most relevant for drug products.

950   **Safety Limiting Toxicity**

951   Inorganic arsenic has shown to be genotoxic, but not mutagenic and has been
952   acknowledged as a human carcinogen (Group 1; IARC, 2012).

953   Due to its ubiquitous nature and toxicity profile, there have been many risk assessments
954   conducted of arsenic and arsenic compounds, which utilize non-threshold, linear dose
955   response approaches (Meharg and Raab, 2010).

956   The effects of arsenic in humans for the most part have not been reproduced in animals,
957   so the risk assessments have to rely heavily upon epidemiology data in populations with
958   high exposure concentrations (Schuhmacher-Wolz *et al.* 2009). In humans, both cancer
959   and non-cancer effects have been linked to arsenic exposure. Oral exposure has been
960   linked to cancers of the skin, liver, lung, kidney and bladder. Following inhalation
961   exposure there is evidence for an increased risk of lung cancer (ATSDR, 2007; IARC,
962   2012; EU EFSA, 2009; WHO, 2011; US EPA, 2010).

963   The skin (dyspigmentation, palmoplantar keratosis) and gastrointestinal tract (e.g.,
964   nausea) appear to be the most sensitive targets for non-cancer adverse effects after oral
965   ingestion while vascular disease, reproductive effects and neurological effects are also
966   reported as non-cancer endpoints (IARC, 2012; Schuhmacher-Wolz *et al.* 2009; US EPA,
967   2007). Oral exposure studies suggest that skin lesions may appear at levels above 0.02
968   mg As/kg/day; no effects were generally seen at levels from 0.0004 to 0.01 mg As/kg/day
969   (ATSDR, 2007). There are insufficient epidemiological data to set a LOEL or NOEL for
970   other endpoints. The regions of hyperkeratosis may evolve into skin cancers (ATSDR,
971   2007) and can possibly be considered predictive of skin and internal cancers and the non-
972   cancer long-term adverse health effects (Chen *et al.* 2005; Hsu *et al.* 2013; Ahsan and
973   Steinmaus, 2013).

974   Studies of large populations (~40,000) exposed to arsenic concentrations in well water at
975   1000 µg/L and higher in southwestern Chinese Taipei have been the basis of risk
976   assessments of skin cancer, and more recently of bladder and lung cancer (US EPA,
977   2010). Recent meta-analyses of cancer risk have indicated no additional bladder cancer
978   risk at low dose exposure (<100–200 µg/L) (Chu and Crawford-Brown, 2006, 2007; Mink
979   *et al.* 2008). This is consistent with the work of Schuhmacher-Wolz *et al.* (2009).

980   The inhalation unit risk for cancer is 0.0043 per µg/m^3 has been established by the US
981   EPA based on data from two US smelters (US EPA, 2007). The Texas Commission on
982   Environmental Quality provided an update to the US EPA Unit Risk Factor (URF),
983   incorporating additional years of follow-up to the US EPA data and additional data on

984 workers from the United Kingdom and Sweden, and calculated a URF of 0.0015 per
985 μg/m³. This URF translates to an air concentration of 0.067 μg/m³ at a risk of 1 in
986 100,000 excess lung cancer mortality (Erraguntla *et al.* 2012).

987 **PDE – Oral Exposure**

988 The oral PDE is based on the chronic effects of As to skin and sets the limit at 15 μg/day
989 based on ATSDR Minimal Risk Level (MRL) and US EPA limit of 0.0003 mg/kg/day
990 (ATSDR, 2007; US EPA 2007; EU EFSA, 2009). The PDE calculated based on the
991 ATSDR MRL is consistent with drinking water standards (WHO, 2011).

992 0.0003 mg/kg/day x 50 kg human = 0.015 mg/day = 15 μg/day.

993 No modifying factors were applied because they are incorporated into the derivation of
994 the MRL.

995 **PDE – Parenteral Exposure**

996 The oral bioavailability of As is ~95%. The most direct evidence is from a study that
997 evaluated the 6-day elimination of arsenic in healthy humans who were given water
998 from a high-arsenic sampling site (arsenic species not specified) and that reported
999 approximately 95% absorption (Zheng *et al.* 2002). Therefore the PDE is identical to the
1000 oral PDE.

1001 PDE = 15 μg/day.

1002 **PDE – Inhalation Exposure**

1003 Increased risk of lung cancer and other respiratory disorders have been reported
1004 following inhalation exposure to workers in the occupational setting. The rationale for
1005 using a cancer endpoint for inhalation to set the PDE is the relative lack of information
1006 on linear-dose extrapolation, as compared to the oral route. No modifying factors are
1007 needed as the URF were determined for the protection of the general public. Based on
1008 the assessment conducted by Erraguntla *et al.* (2012), based on the risk of 1:100.000, the
1009 inhalation PDE is:

1010 0.067 μg/m³ ÷ 1000 L/m³ x 28800 L/d = 1.9 μg/d.

1011 No modifying factors were applied because the PDE is based on the multiplicate relative
1012 risk model described by Erraguntla *et al.* (2012).

1013 **REFERENCES**

1014 Ahsan H, Steinmaus C. Invited commentary: use of arsenical skin lesions to predict risk
1015 of internal cancer-implications for prevention and future research. Am J Epidemiol
1016 2013;177:213-16.

1017 ATSDR. Toxicological profile for arsenic. Agency for Toxic Substances and Disease
1018 Registry, Public Health Service, U.S. Department of Health and Human Services,
1019 Atlanta, GA. 2007.

1020 Chen CJ, Hsu LI, Wang CH, Shih WL, Hsu YH, Tseng MP, et al. Biomarkers of exposure,
1021 effect, and susceptibility of arsenic-induced health hazards in Taiwan. Toxicol Appl
1022 Pharmacol 2005; 206:198-206.

1023 Chu HA, Crawford-Brown DJ. Inorganic arsenic in drinking water and bladder cancer: a
1024 metaanalysis for dose-response assessment. Int J Environ Res Public Health 2006;3:316-
1025 22.

1026 Chu HA, Crawford-Brown DJ. Inorganic arsenic in drinking water and bladder cancer: a
1027 metaanalysis for dose-response assessment. Int J Environ Res Public Health 2007;4:340-
1028 41.

1029 Erraguntla NK, Sielken RL Jr, Valdez-Flores C, Grant RL. An updated inhalation unit
1030 risk factor for arsenic and inorganic arsenic compounds based on a combined analysis of
1031 epidemiology studies. Regul Toxicol Pharmacol 2012;64: 329-41.

1032 EU EFSA. Scientific opinion on arsenic in food. European Food Safety Authority. EFSA
1033 Journal 2009;7(10):1351.

1034 Hsu LI, Chen GS, Lee CH, Yang TY, Chen YH, Wang YH, et al. Use of arsenic-induced
1035 palmoplantar hyperkeratosis and skin cancers to predict risk of subsequent internal
1036 malignancy. Am J Epidemiol 2013;173:202-12.

1037 IARC. Arsenic, metals, fibres, and dusts: a review of human carcinogens. Monographs on
1038 the Evaluation of Carcinogenic Risks to Humans. International Agency for Research on
1039 Cancer, World Health Organization, Lyon. 2012;100C.

1040 Meharg AA, Raab A. Getting to the bottom of arsenic standards and guidelines. Environ
1041 Sci Technol 2010;44:4395-99.

1042 Mink PJ, Alexander DD, Barraj LM, Kelsh MA, Tsuji JS. Low-level arsenic exposure in
1043 drinking water and bladder cancer: a review and meta-analysis. Regul Toxicol
1044 Pharmacol 2008;58:299-310.

1045 Schuhmacher-Wolz U, Dieter HH, Klein D, Schneider K. Oral exposure to inorganic
1046 arsenic: and evaluation of its carcinogenic and non-carcinogenic effects. Crit Rev Toxicol
1047 2009;39:271-98.

1048 US EPA. Arsenic, inorganic. Integrated Risk Information System (IRIS). 1998.

1049 US EPA. Inorganic arsenic. TEACH Chemical Summary. 2007.

1050 US EPA. Toxicological review of inorganic arsenic (CAS No. 7440-38-2). In support of
1051 summary information on the Integrated Risk Information System (IRIS). 2010.

1052 WHO. Arsenic in drinking-water. Background document of development of WHO
1053 Guidelines for Drinking-water quality. World Health Organization. 2011.

1054 Zheng Y, Wu J, Ng JC, Wang G, Lian W. The absorption and excretion of fluoride and
1055 arsenic in humans. Toxicol Lett 2002;133:77-82.

1056 **BARIUM**

1057 **Summary of PDE for Barium**

Barium (Ba)			
	Oral	Parenteral	Inhalation
PDE (µg/day)	13000	1300	340

1058 **Introduction**

1059 Barium (Ba) is a dense, silver-white, soft alkaline earth metal that oxidizes readily in
1060 moist air and reacts with water. The Ba^{2+} ion and the water soluble compounds of Ba
1061 (chloride, nitrate, hydroxide) are toxic. The insoluble compounds of barium, such as
1062 barium sulfate, do not generate free Ba^{2+} ions in the gastrointestinal tract and therefore
1063 are generally nontoxic to humans. Ba is nutritionally not essential and no metabolic
1064 function is known. Barium sulfate is used as a support for catalyst (e.g., Pd).

1065 **Safety Limiting Toxicity**

1066 In animals and humans, the kidney appears to be the most sensitive target of toxicity
1067 resulting from repeated ingestion of soluble Ba salts. Chronic rodent studies support the
1068 evidence for an association between Ba exposure and renal toxicity. In humans, repeated
1069 exposure to Ba oxide *via* inhalation may cause bronchitis, including cough, phlegm,
1070 and/or shortness of breath.

1071 **PDE – Oral Exposure**

1072 Mice and rat Ba drinking water studies have been conducted (NTP, 1994). Based on the
1073 review of these data, the mouse was determined to be the more sensitive species. The 2-
1074 year drinking water study in mice with barium chloride dihydrate was selected as the
1075 principal study and compound-related nephropathy was identified as the critical effect
1076 for deriving a PDE for Ba and its soluble salts. The lesions were characterized by tubule
1077 dilatation, renal tubule atrophy, tubule cell regeneration, hyaline cast formation,
1078 multifocal interstitial fibrosis, and the presence of crystals, primarily in the lumen of the
1079 renal tubules. These changes were characterized as morphologically distinct from the
1080 spontaneous degenerative renal lesions commonly observed in aging mice.

1081 The oral PDE was determined on the basis of the NOAEL of 500 mg/L (equivalent to 30
1082 mg Ba/kg/day), using the modifying factors (F1-F5 as discussed in Appendix 1).

1083 PDE = 30 mg/kg/day x 50 kg / 12 x 10 x 1 x 1 x 1 = 12.5 mg/day ~13.000 µg/day.

1084 **PDE – Parenteral Exposure**

1085 No relevant data on parenteral exposure to barium compounds were found. The
1086 bioavailability of Ba is estimated to be 20 – 60% in adults and infants, respectively
1087 (ATSDR, 2007). Thus, a modifying factor of 10 of the oral PDE was used.

1088 PDE = 13.000 µg/day/ 10 = 1300 µg/day.

1089 **PDE – Inhalation Exposure**

1090 No relevant data on inhalation exposure to barium compounds were found. US DoL
1091 (2013) has a reported TWA of 0.5 mg/m^3 based on soluble Ba salts.
1092
1093 Taking into account the modifying factors (F1-F5 as discussed in Appendix 1), the
1094 inhalation PDE is calculated as:
1095

1096   For continuous dosing = $\underline{500\ \mu g/\ m^3\ x\ 8\ hr/day\ x\ 5\ days/week}$
1097   24 hr/day x 7 days/week X 1000 L/m^3

1098   =   0.119 µg/L

1099   Daily dose = $\underline{0.119\ \mu g/L\ \ x\ 28800\ L}$ = 68.6 µg/kg
1100   50 kg

1101   PDE = $\underline{68.6\ \mu g/kg\ x\ 50\ kg}$ =   343 µg/day ~340 µg/day.
1102   1 x 10 x 1 x 1 x 1

1103   **REFERENCES**

1104   ATSDR. Toxicological profile for barium and barium compounds. Agency for Toxic
1105   Substances and Disease Registry, Public Health Service, U.S. Department of Health and
1106   Human Services, Atlanta, GA. 2007.

1107   NTP. Technical report on the toxicology and carcinogenesis studies of barium chloride
1108   dihydrate (CAS No. 10326-27-9) in F344/N rats and B6C3F1 mice (drinking water
1109   studies). National Toxicology Program, Public Health Service, U.S. Department of
1110   Health and Human Services, Research Triangle Park, NC. 1994;NTP TR 432.

1111   US DoL (OHSA). 29 CRF 1910.1000 Table Z-1. Limits for air contaminants. U.S.
1112   Department of Labor. 2013.

1113 **CADMIUM**

1114 **Summary of PDE for Cadmium**

Cadmium (Cd)			
	Oral	Parenteral	Inhalation
PDE (µg/day)	5.0	6.0	3.4

1115 **Introduction**

1116 Cadmium (Cd) is a transition metal whose most abundant naturally-occurring isotope is
1117 non-radioactive. It is found in nature in mineral forms and is obtained for commercial
1118 uses principally from cadmium ore (ATSDR, 2012). Cadmium exists as a salt form in the
1119 +2 oxidation state only. Some cadmium salts are water soluble such as cadmium chloride,
1120 cadmium sulfate and cadmium nitrate; other insoluble salts can become more soluble by
1121 interaction with acids, light or oxygen. Cadmium, cadmium oxide, cadmium salts on
1122 borosilicate carrier are used as catalysts in organic synthesis. Silver cadmium alloy is
1123 used in the selective hydrogenation of carbonyl compounds.

1124 **Safety Limiting Toxicity**

1125 Cadmium has shown to be genotoxic, but not mutagenic and has been acknowledged as a
1126 human carcinogen (Group 1; IARC, 2012). Cadmium and cadmium compounds cause
1127 cancer of the lung. Also, positive associations have been observed between exposure to
1128 cadmium and cadmium compounds and cancer of the kidney and of the prostate.

1129 A sensitive endpoint for oral exposure to cadmium and cadmium salts is renal toxicity
1130 (Buchet *et al.* 1990). Skeletal and renal effects are observed at similar exposure levels
1131 and are a sensitive marker of cadmium exposure (ATSDR, 2012).

1132 Evidence from numerous epidemiologic studies assessing inhalation exposures to
1133 cadmium *via* both occupational and environmental routes has demonstrated an
1134 increased risk of developing cancer (primarily lung) that correlates with inhalation
1135 exposure to cadmium (IARC, 2012; NTP, 2004).

1136 **PDE – Oral Exposure**

1137 A sensitive endpoint for oral exposure to cadmium and cadmium salts is renal toxicity
1138 (Buchet *et al.* 1990). Skeletal and renal effects are observed at similar exposure levels
1139 and are a sensitive marker of cadmium exposure (ATSDR, 2012). A number of oral
1140 exposure studies of cadmium in rats and mice showed no evidence of carcinogenicity.
1141 Therefore the renal toxicity endpoint was used to establish the oral PDE for cadmium,
1142 following the recommendations of ATSDR, a level of 0.1 µg/kg for chronic exposure is
1143 used to set the oral PDE. This is in line with the WHO drinking water limit of 0.003
1144 mg/L/day (WHO 2011).

1145 Taking into account the modifying factors (F1-F5 as discussed in Appendix 1), the oral
1146 PDE is calculated as:

1147 PDE = 0.1 µg/kg/day x 50 kg = 5.0 µg/day.

PDE – Parenteral Exposure

12 week study in rats given daily subcutaneous injections of 0.6 mg/kg Cd, 5 days per week showed renal damage at week 7 and later (Prozialeck, 2009). The LOAEL of this study is 0.6 mg/kg.

Taking into account the modifying factors (F1-F5 as discussed in Appendix 1), the parenteral PDE is calculated as:

PDE = 0.6 mg/kg/day x 50 kg / 5 x 10 x 5 x 10 x 2 = 6.0 µg/day.

F4 was chosen as 10 because cadmium is carcinogenic by the inhalation route. F5 was set at 2, since no NOAEL was identified in this study.

PDE – Inhalation Exposure

The use of 5 µg/m^3 as the PEL (US DoL, 2013) was considered acceptable as cadmium is non-mutagenic. This PDE is similar to the quantitative estimate of carcinogenic risk from inhalation exposure to cadmium (1:10·000 risk, US EPA, 1992; EU SCOEL, 2010).

Taking into account the modifying factors (F1-F5 as discussed in Appendix 1), the inhalation PDE is calculated as:

For continuous dosing = 5 µg/m^3 ÷1000 L/m^3 = 0.005 µg/L

0.005 µg/L x 8 hours x 5 days ÷ 24 hours x 7 days = 0.0012 µg/L

Daily Dose = 0.0012 µg/L x 28800 L/day ÷ 50 kg = 0.69 µg/kg

PDE = 0.69 µg/kg x 50 kg / 1 x 10 x 1 x 1 x 1 = 3.4 µg/day.

A modifying factor F2 of 10 was applied to cover the full population with the data coming from the worker population.

REFERENCES

ATSDR. Toxicological profile of cadmium. Agency for Toxic Substances and Disease Registry, Public Health Service, U.S. Department of Health and Human Services, Atlanta, GA. 2012.

Buchet JP, Lauwerys R, Roels H, Bernard A, Bruaux P, Claeys F, et al. Renal effects of cadmium body burden of the general population. Lancet 1990;336:699-702.

EU SCOEL. Recommendation from the scientific committee on occupational exposure limits for cadmium and its inorganic compounds. European Union Scientific Committee on Occupational Exposure Limits. 2010;SCOEL/SUM/136.

IARC. Arsenic, metals, fibres, and dusts: a review of human carcinogens. Monographs on the Evaluation of Carcinogenic Risks to Humans. International Agency for Research on Cancer, World Health Organization, Lyon. 2012;100C.

NTP. Technical report on toxicity studies of cadmium oxide (CAS No. 1306-19-0) administered by inhalation to F344/N Rats and B6C3F1 mice. National Toxicology Program, Public Health Service, U.S. Department of Health and Human Services. 2004.

Prozialeck WC, Edwards JR, Vaidya VS, Bonventre JV. Preclinical evaluation of novel urinary biomarkers of cadmium nephrotoxicity. Toxicol Appl Pharmacol 2009;238:301-305.

US EPA. Cadmium. Integrated Risk Information System (IRIS). 1992.

US DoL (OHSA). 29 CRF 1910.1000 Table Z-1. Limits for air contaminants. U.S. Department of Labor. 2013.

1190   WHO. Cadmium in drinking water. Background document for development of WHO
1191   Guidelines   for   drinking-water   quality.   World   Health   Organization.
1192   2011;WHO/SDE/WSH/03.04/80/Rev/1.

1193 **CHROMIUM**

1194 **Summary of PDE for Chromium**

Chromium (Cr III)			
	Oral	Parenteral	Inhalation
PDE (µg/day)	11000	1100	2.9

1195 **Introduction**

1196 Chromium (Cr) is found in a variety of oxidation states, the most important being Cr 0
1197 (in stainless steel) Cr II, III and VI. Cr II is readily oxidized and is used as a reducing
1198 agent in chemical synthesis. Cr VI is a powerful oxidant, chromate, CrO_4^{2-}, and
1199 dichromate, $Cr_2O_7^{2-}$, being the best known oxyanions. Cr III, the most abundant
1200 environmental form, is an essential element that plays a role in glucose metabolism.
1201 Chromium deficiency causes changes in the metabolism of glucose and lipids and may be
1202 associated with maturity-onset diabetes, cardiovascular diseases, and nervous system
1203 disorders (Anderson, 1993, 1995). Sources of chromium in pharmaceuticals may include
1204 colorants, leaching from equipment or container closure systems, and catalysts. With
1205 the exception of use as a catalyst, intake of chromium from pharmaceuticals will be in
1206 the form of metallic chromium (Cr 0) or Cr III rather than the more toxic Cr VI; therefore,
1207 for drug products, this safety assessment is based on the known toxicity of Cr III and Cr
1208 VI is excluded from this assessment. Chromium present as a colorant (e.g., chromium
1209 oxide green, chromium hydroxide green; see 21 CFR 72) is intentionally added and thus
1210 beyond the scope of this guidance.

1211 **Safety Limiting Toxicity**

1212 The data was reviewed to identify the safety limiting toxicities based on routes of
1213 administration.

1214 **PDE – Oral Exposure**

1215 No specific target organ toxicities have been identified for the oral intake of
1216 chromium. Generally oral intake of 5 mg/kg/day Cr III (US EPA, 1998) is not expected to
1217 be associated with adverse health.

1218 The 2 year NTP studies (2010) on the carcinogenicity of Cr (III) picolinate administered
1219 in feed to rats and mice provided the most relevant safety information for Cr as present
1220 in drug products. The NOAEL was 90 mg/kg Cr (III) picolinate (11.9 weight %; 10.7
1221 mg/kg/day CrIII) in rats based on increase in the incidence of preputial gland adenoma
1222 in male rats at 460 mg/kg. This finding was not dose-dependent and was considered an
1223 equivocal finding by the study authors. This finding was not observed male mice or in
1224 the female counterpart in either species (clitoral gland). In the absence of a treatment-
1225 related carcinogenic finding, F4 was set at 1.

1226 Taking into account the modifying factors (F1-F5 as discussed in Appendix 1), the oral
1227 PDE is calculated as:

1228 PDE = 10.7 mg/kg/day x 50 kg/ 5 x 10 x 1 x 1 x 1 = 10.7 mg/day ~11000 µg/day.

1229 **PDE – Parenteral Exposure**

1230 Recommendation for the nutritional intravenous administration of Chromium (III) vary
1231 per age group between 0.05 µg/kg/day in preterm infants and 15 µg/kg in adults
1232 (Moukazel, 2009). There is insufficient information to assess if exceeding these

1233 recommended daily doses may lead to adverse responses e.g., for the kidney especially in
1234 newborns and preterm infants.

1235 The safety review for Cr was unable to identify any significant assessments upon which
1236 to calculate a PDE for parenteral routes of exposure. On the basis of an oral
1237 bioavailability of about 10% for chromium and inorganic chromium compounds (ATSDR,
1238 2012), the recommended PDE for chromium for a parenteral exposure is:

1239 PDE = 11000 µg/day/10 = 1100 µg/day.

1240 **PDE – Inhalation Exposure**

1241 The study by Deralenko (1999) used inhalation of Cr (III) sulfate particles during 13
1242 weeks (6h/day and 5 days per week) causing predominantly chronic inflammation of the
1243 airways (mononuclear infiltrate, particular material) and locally thickening of alveolar
1244 walls. The effect was observed at all doses. The LOAEL is 17 mg/m^3 (3 mg CrIII/m^3). A
1245 lack of systemic toxicity was noted in a 13 week inhalation study in rats administered
1246 soluble or insoluble Cr (III). Based on these data the on these data, the inhalation MRL
1247 of 0. 1µg/m^3 was used to set the PDE (ATSDR, 2012).

1248 PDE =0.0001 mg/ m^3 /1000 m^3/L x 28800 L/day = 2.9 µg/day.

1249 **REFERENCES**

1250 Anderson RA. Recent advances in the clinical and biochemical effects of chromium
1251 deficiency. Prog Clin Biol Res 1993;380:221-34.

1252 Anderson RA. Chromium and parenteral nutrition. Nutr 1995;11(1 suppl.):83-6.

1253 ATSDR. Toxicological profile of chromium. Agency for Toxic Substances and Disease
1254 Registry, Public Health Service, U.S. Department of Health and Human Services,
1255 Atlanta, GA. 2012.

1256 Derelanko MJ, Rinehart WE, Hilaski RJ, Thompson RB, Löser E. Thirteen week
1257 subchronic rat inhalation toxicity study with a recovery phase of trivalent chromium
1258 compounds, chromic oxide, and basic chromium sulfate. Toxicol Sci 1999;52:278-88.

1259 Glaser U, Hochrainer D, Klöppel H, Oldiges H. Carcinogenicity of sodium dichromate
1260 and chromium (VI/III) oxide aerosols inhaled by male Wistar rats. Toxicology. 1986;42(2-
1261 3):219-32.

1262 Moukarzel A. Chromium in parenteral nutrition: too little or too much. Gastroenterology
1263 2009;137:S18-S28.

1264 NTP. Technical report on the toxicology and carcinogenesis studies of chromium
1265 picolinate monohydrate in F344/N rats and B6C3F1 mice. National Toxicology Program,
1266 Public Health Service, U.S. Department of Health and Human Services. 2010;NTP TR
1267 556.

1268 US DoL (OHSA). 29 CRF 1910.1000 Table Z-1. Limits for air contaminants. U.S.
1269 Department of Labor. 2013.

1270 US EPA. Chromium (III), insoluble salts. Integrated Risk Information System (IRIS).
1271 1998.

1272   **COBALT**

1273   **Summary of PDE for Cobalt**

Cobalt (Co)			
	Oral	Parenteral	Inhalation
PDE (µg/day)	50	5.0	2.9

1274   **Introduction**

1275   Cobalt (Co) is a naturally-occurring element, often combined with other elements such as
1276   oxygen, sulfur, and arsenic. Co is essential in the human body because it is an integral
1277   component of Vitamin B-12 and functions as a co-enzyme for several enzymes critical in
1278   the synthesis of hemoglobin and the prevention of pernicious anemia. The Recommended
1279   Dietary Allowance of vitamin B12 is 2.4 µg/day, which corresponds to 0.1 µg of Co. No
1280   essential biological function of inorganic Co in the human body has been identified.
1281   Cobalt compounds (e.g., cobalt octoate) are being used as catalysts in selective
1282   hydrogenation.

1283   **Safety Limiting Toxicity**

1284   The IARC (2006) concluded that Co sulphate and other soluble Co (II) salts are possible
1285   human carcinogens (Group 2B). The data indicate the location of tumors is limited to the
1286   lung in rats and humans.

1287   Polycythemia is considered to be the most sensitive finding after repeated oral exposure
1288   to humans. Inhalation exposure of humans to Co has been associated with a severe and
1289   progressive respiratory disease known as hard-metal pneumoconiosis, as well as asthma
1290   and contact dermatitis.

1291   **PDE – Oral Exposure**

1292   The oral PDE is based on the available human data. Polycythemia was the most
1293   sensitive finding in humans after repeated oral exposure to 150 mg of cobalt chloride
1294   (~1 mg Co /kg/day). The oral PDE was determined on the basis of the LOAEL of 1
1295   mg/kg/day in male human volunteers after oral exposure over a period of 22 days (WHO,
1296   2006).

1297   Taking into account the modifying factors (F1-F5 as discussed in Appendix 1), the oral
1298   PDE is calculated as below:

1299   PDE = 1 mg/kg/day x 50 kg / 1 x 10 x 10 x 1 x 10 = 0.05 mg/day = 50 µg/day.

1300   **PDE – Parenteral Exposure**

1301   No relevant data on parenteral exposure to cobalt compounds were found. On the basis of
1302   the oral bioavailability ranging largely from 18-97% for cobalt and inorganic cobalt
1303   compounds (ATSDR, 2004). Using a safety factor of 10 to account for low bioavailability,
1304   the PDE for cobalt for parenteral exposure is:

1305   PDE = 50 µg/day / 10 = 5.0 µg/day.

1306   **PDE – Inhalation Exposure**

1307   Co sulphate and other soluble Co (II) salts are possible human carcinogens (Group 2B)
1308   which can induce lung tumors.

1309 Pneumoconiosis, asthma and contact dermatitis were the principal non-carcinogenic
1310 effects in humans after chronic inhalation. For the calculation of the inhalation PDE, the
1311 chronic inhalation MRL of 0.1 microgram / m^3 was used (ATSDR, 2010).

1312 0.0001 mg/ m^3 /1000 m^3/L x 28800 L/day = 2.9 µg/day.

1313 **REFERENCES**

1314 ATSDR. Toxicological profile for cobalt. Agency for Toxic Substances and Disease
1315 Registry, Public Health Service, U.S. Department of Health and Human Services,
1316 Atlanta, GA. 2010.

1317 IARC. Cobalt in hard metals and cobalt sulfate, gallium arsenide, indium phosphide and
1318 vanadium pentoxide. International Agency for Research on Cancer, World Health
1319 Organization, Lyon. 2003;86, updated in 2006.

1320 WHO. Cobalt and inorganic cobalt compounds. Concise International Chemical
1321 Assessment Document. Inter-Organization Programme for the Sound Management of
1322 Chemicals (IOMC). World Health Organization. 2006;69.

1323

1324 **COPPER**

1325 **Summary of PDE for Copper**

Copper (Cu)			
	Oral	Parenteral	Inhalation
PDE (µg/day)	1300	130	13

1326 **Introduction**

1327 Copper (Cu) is a Group 11 element of the first transition series and has two main
1328 oxidation states, Cu I and Cu II. It is an essential trace element in both animals and
1329 humans. Copper plays a vital role in a number of critical enzyme systems and is closely
1330 linked with normal hematopoiesis and cellular metabolism. Copper compounds (e.g.,
1331 copper chromite) are being used as catalysts in hydrogenolysis and decarboxylation
1332 reactions

1333 **Safety Limiting Toxicity**

1334 A general review of relevant safety data for animals and humans indicates that copper
1335 can produce adverse effects to the gastrointestinal tract, liver, and kidney upon ingestion
1336 of toxic doses (Araya *et al.* 2003).

1337 **PDE – Oral Exposure**

1338 Studies on cupric sulfate and copper 8-quinolinolate have been conducted in mice and
1339 rats and dogs (EHC, 1998). Rats were determined to be the more sensitive species to
1340 effects on liver and kidney. In a 13 week study in rats the NOAEL was 17 mg/kg/day for
1341 copper sulfate, equivalent to 6.7 mg Cu/kg/day (Hebert, 1993).

1342 Taking into account the modifying factors (F1-F5 as discussed in Appendix 1), the oral
1343 PDE is calculated as:

1344 PDE = 6.7 mg/kg/day x 50 kg / 5 x 10 x 5 x 1 x 1 = 1.34 mg/day = 1340 µg/day ~1300
1345 µg/day.

1346 **PDE – Parenteral Exposure**

1347 The safety review for copper was unable to identify any significant assessments upon
1348 which to calculate a PDE for parenteral routes of exposure. The human gastrointestinal
1349 system can absorb 30-40% of ingested copper from the typical diets consumed in
1350 industrialised countries (Wapnir, 1998). On the basis of limited oral bioavailability of
1351 30%-40% for copper and inorganic copper salts, the recommended PDE for copper for
1352 parenteral exposure is:
1353 PDE = 1340 µg/day / 10 = 134 µg/day ~130 µg/day.

1354 **PDE – Inhalation Exposure**

1355 The available data on the toxicity of inhaled copper were considered inadequate for
1356 derivation of acute-, intermediate-, or chronic-duration inhalation MRLs (ATSDR, 2004).

1357 The inhalation PDE was calculated by dividing the oral PDE by 100 (as described in
1358 Section 3.1).

1359 1340/100 = 13.4 µg/day ~13 µg/day.

1360

REFERENCES

Araya M, Olivares M, Pizarro F, González M, Speisky H, Uauy R. Gastrointestinal symptoms and blood indicators of copper load in apparently healthy adults undergoing controlled copper exposure. Am J Clin Nutr 2003;77(3):646-50.

ATSDR. Profile for copper. Agency for Toxic Substances and Disease Registry, Public Health Service, U.S. Department of Health and Human Services, Atlanta, GA. 2004

Hébert CD, Elwell MR, Travlos GS, Fitz CJ, Bucher JR. Subchronic toxicity of cupric sulfate administered in drinking water and feed to rats and mice. Fundam Appl Toxicol 1993;21:461-75.

IPCS. Copper. Environmental Health Criteria 200. International Programme on Chemical Safety. World Health Organization, Geneva. 1998.

Wapnir RA. Copper absorption and bioavailability. Am J Clin Nutr 1998;67(suppl):1054S-60S.

WHO. Copper – toxicological evaluation of certain food additives. WHO Food Additive Series 17 1982. World Health Organization.

1376   **GOLD**

1377   **Summary of PDE for Gold**

Gold (Au)			
	Oral	Parenteral	Inhalation
PDE (µg/day)	130	130	1.3

1378   **Introduction**

1379   Gold (Au) exists in metallic form and in oxidation states of +1 to +5, the monovalent and
1380   trivalent forms being the most common. Elemental gold is poorly absorbed and
1381   consequently is not considered biologically active. Gold is being used on a carrier or in
1382   complexes like gold chloride and L–Au$^+$ (where L is a phosphane, phosphite, or an arsine;
1383   Telles, 1998), as catalysts in organic synthesis. The only source for gold in drug products
1384   comes from the use as catalyst. Gold (I) salts are used therapeutically.

1385   **Safety Limiting Toxicity**

1386   Most knowledge of gold toxicity is based on therapeutic uses of gold. Currently available
1387   therapies are gold salts of monovalent gold (I) with a sulfur ligand (Au-S), but metallic
1388   gold has also been studied. No toxicity was seen in 10 patients administered colloidal
1389   metallic gold (monoatomic gold) at 30 mg/day for one week followed by 60 mg/day the
1390   second week or the reverse schedule. The patients were continued on trial for an
1391   additional 2 years at 30 mg/day. There was no evidence of hematologic, renal or hepatic
1392   cytotoxicity but some improvement in clinical symptoms of rheumatoid arthritis and in
1393   cytokine parameters were noted (Abraham and Himmel, 1997).

1394   Long term animal data are available with Au compounds. However, these studies have
1395   been performed with monovalent gold Au I and are not considered sufficiently relevant to
1396   assess the potential toxicity of Au in pharmaceutical products.

1397   Au (III) is thought to be the more toxic form and is used in catalysis, e.g., as gold
1398   trichloride. There is only limited data on gold (III) complexes. In one study, the gold (III)
1399   compound [Au(en)Cl$_2$]Cl (dichloro(ethylenediamine-aurate(III) ion) caused minimal
1400   histological changes in the kidney and liver of rats, and no renal tubular necrosis, at a
1401   dose of 32.2 mg/kg in mice administered the compound intraperitoneally for 14 days
1402   (Ahmed *et al.* 2012).

1403   **PDE – Oral Exposure**

1404   The toxicologically significant endpoint for gold exposures is renal toxicity.

1405   Taking into account the modifying factors (F1-F5 as discussed in Appendix 1), the oral
1406   PDE is calculated as:

1407   PDE = 32.2 mg/kg x 50 kg / 12 x 10 x 10 x 1 x 10 = 134 µg/day ~130 µg/day.

1408   F5 was put at 10 because the NOAEL was not established and the toxicological
1409   assessment was not complete.

1410   **PDE – Parenteral Exposure**

1411   In humans, 50 mg intramuscular (IM) injections of gold sodium thiomalate resulted in
1412   >95% bioavailability (Blocka, 1986). In rabbits, ~70 % of the gold sodium thiomalate was
1413   absorbed after an IM injection of 2/mg/kg (Melethil, 1987).

1414   Based on high bioavailability, the parenteral PDE is equivalent to the oral PDE.

1415   PDE = 130 μg/day.

1416   **PDE – Inhalation Exposure**

1417   In the absence of relevant inhalation and parenteral data, a modifying factor of 100 was
1418   applied to the oral PDE as described in Section 3.1.

1419   PDE = 134 /100 = 1.34 μg/day ~1.3 μg/day.

1420   **REFERENCES**

1421   Abraham GE, Himmel PB. Management of rheumatoid arthritis: rationale for the use of
1422   colloidal metallic gold. J Nutr Environ Med 1997;7:295-305.

1423   Ahmed A, Al Tamimi DM, Isab AA, Alkhawajah AMM, Shawarby MA. Histological
1424   changes in kidney and liver of rats due to gold (III) compound $[Au(en)Cl_2]Cl$. PLoS ONE
1425   2012;7(12):1-11.

1426   Blocka KL, Paulus HE, Furst DE. Clinical pharmacokinetics of oral and injectable gold
1427   compounds. Clin Pharmacokinet 1986;11:133-43.

1428   Melethil S, Schoepp D. Pharmacokinetics of gold sodium thiomalate in rabbits. Pharm
1429   Res 1987;4(4):332-6.

1430   Telles JH, Brode S, Chabanas M. Cationic gold (I) complexes: highly efficient catalysts
1431   for the addition of alcohols to alkynes. Angew Chem Int Ed 1998;37:1415-18.

1432   **LEAD**

1433   **Summary of PDE for Lead**

Lead (Pb)			
	Oral	Parenteral	Inhalation
PDE (µg/day)	5.0	5.0	5.0

1434   **Introduction**

1435   Lead (Pb) is the most common heavy element. It occurs in organic and inorganic forms.
1436   The generally bivalent Pb compounds include water-soluble salts such as Pb acetate as
1437   well as insoluble salts such as Pb oxides. Organic Pb compounds include the gasoline
1438   additives tetramethyl- and tetraethyl-lead. Organic Pb compounds undergo fairly rapid
1439   degradation in the atmosphere and form persistent inorganic Pb compounds in water
1440   and soil. Pb has no known useful biological function in human or mammalian organisms
1441   (ATSDR, 2007).

1442   **Safety Limiting Toxicity**

1443   In humans and animals, exposure to Pb may cause neurological, reproductive,
1444   developmental, immune, cardiovascular and renal health effects. In general, sensitivity
1445   to Pb toxicity is greater when there is exposure *in utero* and in children compared to
1446   adults. A target blood level of 1-2 µg/dL was set, and using modelling programs (US EPA,
1447   2009) that assumed 100% bioavailability and no other exposure, a PDE was obtained.
1448   For this reason, the PDEs are the same regardless of the route of administration.

1449   **PDE – Oral Exposure**

1450   Adverse neurobehavioral effects are considered to be the most sensitive and most
1451   relevant endpoint in humans after oral exposure. Data from epidemiological studies
1452   show that blood Pb levels <5 µg/dL may be associated with neurobehavioral deficits in
1453   children (NTP, 2011).

1454   According to the US EPA model (Integrated Exposure Uptake Biokinetic (IEUBK) Model,
1455   1994) (100% absorption, no other sources of lead), oral intake of 5 µg/day translates into
1456   a blood level of 1-2 µg/dL for children age 0-7 years (0-82 months).

1457   PDE = 5.0 µg/day.

1458   **PDE – Parenteral Exposure**

1459   The oral effects of Pb are based on blood levels. Therefore, the parenteral PDE is equal
1460   to the oral PDE of 5.0 µg/day.

1461   **PDE – Inhalation Exposure**

1462   The oral effects of Pb are based on blood levels. Therefore, the inhalation PDE is equal
1463   to the oral PDE of 5.0 µg/day.

1464   **REFERENCES**

1465   ATSDR. Toxicological profile for lead. Agency for Toxic Substances and Disease Registry,
1466   Public Health Service, U.S. Department of Health and Human Services, Atlanta, GA.
1467   2007.

1468   NTP. Monograph on health effects of low-level lead. National Toxicology Program, U.S.
1469   Department of Health and Human Services. 2011.

1470   US EPA. Integrated Exposure Uptake Biokinetic (IEUBK) Model for Lead. 1994,
1471   updated 2009.

1472 **LITHIUM**

1473 **Summary of PDE for Lithium**

Lithium (Li)			
	Oral	Parenteral	Inhalation
PDE (µg/day)	780	390	25

1474 **Introduction**

1475 Lithium (Li) is a common metal that is present in plant and animal tissues. Lithium is
1476 used as a therapeutic agent to treat bipolar disease. Lithium is being used alone or in
1477 combination with other metals as catalyst. Lithium compounds (e.g., lithium aluminum
1478 hydride) are being used as reagents in organic synthesis.

1479 Lithium exists commonly as a salt in the +1 form oxidation state only.

1480 **Safety Limiting Toxicity**

1481 The data was reviewed to identify the safety limiting toxicities based on routes of
1482 administration.

1483 **PDE – Oral Exposure**

1484 There is a minimal amount of data on the effects of lithium carbonate on the immune
1485 system. A 14 day mouse study was conducted to assess the effects of lithium carbonate
1486 on the immune system (NTP, 1986). Doses were modified to 100, 300 and 400 mg/kg in
1487 repeat and later studies because of a lack of effect at 50 and 200 mg/kg. Findings
1488 included dose-dependent effects on decreased in liver and thymus weight, and changes in
1489 leukocytes and red blood cells and associated parameters.

1490 Using 200 mg/kg/day (18.7 mg Li/kg/day) as the NOAEL and modifying factors (F1-F5 as
1491 discussed in Appendix 1), the PDE is:

1492 PDE = 18.7 mg/kg/day x 50 kg/ 12 x 10 x 10 x 1 x 1 = 0.78 mg/day = 780 µg/day.

1493 **PDE – Parenteral Exposure**

1494 There are no adequate data to develop a parenteral PDE. However, based on oral
1495 bioavailability of 85% (Grandjean, 2009) and using a modifying factor of 2, the parenteral
1496 PDE is calculated as:

1497 PDE = 0.77 mg/day / 2 = 0.39 mg/day =390 µg/day.

1498 **PDE – Inhalation Exposure**

1499 Rabbits were exposed to lithium chloride at 0.6 and1.9 mg/m^3 for 4-8 weeks, 5 days/week
1500 for 6 hours/d (Johansson *et al.* 1988). Lungs were studied by light and electron
1501 microscopy with focus on inflammatory changes. No significant effects were reported, so
1502 the highest dose was used to set the PDE.

1503 Taking into account the modifying factors (F1-F5 as discussed in Appendix 1), the oral
1504 PDE is calculated as:

1505 For continuous dosing: PDE = 1.9 mg/m^3 /1000 L/m^3 = .0019 mg/L

1506 0.0019 mg/L x 6 h/day x 5 days / 24h/day x 7days = 0.000339 mg/L

1507 Daily dose: 0.339 µg/L x 1440 L/day/4 kg = 122.04 µg/kg/day

1508 PDE = 122.04 µg/kg/day x 50kg /2.5x10x10x1x1 = 25 µg/day.

1509 **REFERENCES**

1510 Grandjean EM, Aubry JM. Lithium: updated human knowledge using an evidence-based
1511 approach. Part II: Clinical pharmacology and therapeutic monitoring. CNS Drugs
1512 2009;23(4):331-49.

1513 Johansson A, Camner P, Curstedt T, Jarstrand C, Robertson B, Urban T. Rabbit lung
1514 after inhalation of lithium chloride. J Appl Toxicol 1988;8:373-5.

1515 NTP. Immunotoxicity of lithium carbonate in female B6C3F1 mice (CAS No. 554-13-2).
1516 National Toxicology Program, U.S. Department of Health and Human Services.
1517 1986;NTP Report Number IMM85001.

1518 **MERCURY**

1519 **Summary of PDE for Mercury**

Mercury (Hg)			
	Oral	Parenteral	Inhalation
PDE (µg/day)	40	4.0	1.2

1520 **Introduction**

1521 Mercury (Hg) is an element widely existing in the global environment. Hg exists in three
1522 forms: elemental mercury, inorganic mercury and organic mercury. The most likely form
1523 of residual mercury in drug products is the inorganic form. Therefore, this safety
1524 assessment is based on the relevant toxicological data of elemental or inorganic Hg. This
1525 safety assessment and derived PDEs do not apply to organic mercury.

1526 **Safety Limiting Toxicity**

1527 There is no data to indicate that inorganic mercury is carcinogenic in human. There is
1528 limited evidence in experimental animals for the carcinogenicity of mercuric chloride.
1529 IARC concluded that inorganic mercury compounds are not classifiable as to their
1530 carcinogenicity to humans (Group 3; IARC, 1997).

1531 Inorganic mercury compounds show significantly lower oral bioavailability compared to
1532 organic mercury and induce different toxicological effects including neurological,
1533 corrosive, hematopoietic, renal effects and cutaneous disease (acrodynia). The safety
1534 limiting toxicity for inorganic mercury and salts is renal toxicity.

1535 **PDE – Oral Exposure**

1536 There were well organized NTP studies of $HgCl_2$ up to 2 years. The 6 month gavage
1537 study in rats was selected because it had more detailed clinical pathology assessment
1538 and wider range of doses than the 2 year study. Based on adverse renal effects from the
1539 6-months rat study (NTP, 1993), the LOAEL was 0.23 mg/kg/day for mercury (0.16
1540 mg/kg day for mercury when corrected for 7 days of exposure/week).

1541 Using the modifying factors (F1-F5 as discussed in Appendix 1) the oral PDE is
1542 calculated as:

1543 PDE = 0.16 mg/kg /day x 50 kg / 5 x 10 x 2 x 1 x 2 = 0.04 mg/day = 40 µg/day.

1544 F5 was set to 2, because no NOAEL was identified in the study and the effect at the
1545 LOAEL was a slight increase in incidence of an effect also present in the control animals.

1546 **PDE – Parenteral Exposure**

1547 Animal studies indicate that the oral bioavailability of inorganic mercury is in the 10-
1548 30% range (ATSDR, 1999). Therefore, the oral PDE is divided by a factor of 10 (as
1549 described in Section 3.1).

1550 PDE = 40/10 = 4.0 µg/day.

1551 **PDE – Inhalation Exposure**

1552 Neurobehavioral effects are considered to be the most sensitive endpoint following
1553 inhalation exposure in humans as shown in occupational studies at the range of air TWA
1554 levels between 14 and 20 µg/m³ (US EPA, 1995; EU SCOEL, 2007).

1555 The presence of neurobehavioral effects at low-level mercury exposures (14 µg/m³) in
1556 dentists (Ngim *et al.* 1992) indicates that the TWA needs to be considered as a LOAEL.

1557 Taking into account the modifying factors (F1-F5 as discussed in Appendix 1), the
1558 inhalation PDE is calculated based on the long-term inhalation exposure to elemental
1559 mercury vapor:

1560 For continuous dosing = $\dfrac{14 \text{ µg/m}^3 \text{ x 8 hr/day x 6 days/week}}{24 \text{ hr/day x 7 days/week x 1000 L/m}^3}$

1561

1562 $\quad\quad\quad = \quad$ 0.004 µg/L

1563

1564 Daily dose $= \dfrac{0.004 \text{ µg/L x 28800 L}}{50 \text{ kg}} =$ 2.30 µg/kg

1565

1566 PDE $= \dfrac{2.30 \text{ µg/kg x 50 kg}}{1 \text{ x } 10 \text{ x } 1 \text{ x } 1 \text{ x } 10}$ = 1.2 µg/day.
1567

1568 **REFERENCES**

1569 ATSDR. Toxicological profile for mercury. Agency for Toxic Substances and Disease
1570 Registry, Public Health Service, U.S. Department of Health and Human Services,
1571 Atlanta, GA. 1999.

1572 EU SCOEL. Recommendation from the scientific committee on occupational exposure
1573 limits for elemental mercury and inorganic divalent mercury compounds. European
1574 Union Scientific Committee on Occupational Exposure Limits. 2007;SCOEL/SUM/84.

1575 IARC. Beryllium, cadmium, mercury, and exposures in the glass manufacturing industry.
1576 Monographs on the Evaluation of Carcinogenic Risks to Humans. International Agency
1577 for Research on Cancer, World Health Organization, Lyon. 1993;58, updated in 1997.

1578 Ngim CH, Foo SC, Boey KW, and Jeyaratnam J. Chronic neurobehavioural effects of
1579 elemental mercury in dentists. Br J Ind Med 1992;49(11):782-90.

1580 NTP. Technical report on the toxicology and carcinogenesis studies of mercuric chloride
1581 (CAS No. 7487-94-7) in F344 rats and B6C3F1 mice (gavage studies). National
1582 Toxicology Program, Public Health Service, U.S. Department of Health and Human
1583 Services, Research Triangle Park, NC. 1993;NTP TR 408.

1584 US EPA. Mercuric chloride (HgCl₂). Integrated Risk Information System (IRIS). 1995.

1585 WHO. Elemental mercury and inorganic mercury compounds: human health aspects.
1586 Concise International Chemical Assessment Document 50. International Programme on
1587 Chemical Safety (IPCS). World Health Organization. 2003.

1588   **MOLYBDENUM**

1589   **Summary of PDE for Molybdenum**

Molybdenum (Mo)			
	Oral	Parenteral	Inhalation
PDE (µg/day)	180	180	7.6

1590   **Introduction**

1591   The main oxidation states for Mo are IV and VI, the most common forms of which are
1592   oxyanions. The predominant form of Mo occurring in soils and natural waters is the
1593   molybdate ion, MoO_4^{2-} which forms soluble compounds with a variety of cations including
1594 K^+, NH_4^+ and Ca^{2+}. Mo exists in soil in various forms at concentration of 0.1-10 mg/kg.
1595 MoO_2 and MoS_2 are insoluble in water. It is widely present in vegetables, dairy products
1596   and meats. Mo combinations (e.g., Bi-Mo, Fe-Mo, molybdenum oxide and Mo-complexes)
1597   are being used as catalysts in organic synthesis.

1598   Mo deficiency is characterized by night blindness, nausea, disorientation, coma,
1599   tachycardia, tachypnea and associated with various biochemical abnormalities including
1600   high plasma methionine. In addition an almost undetectable serum uric acid
1601   concentration has been reported in a patient receiving total parenteral nutrition
1602   (Abumrad et *al*. 1981).

1603   **Safety Limiting Toxicity**

1604   Molybdenum as the trioxide was not mutagenic (NTP, 1997). Carcinogenicity has not
1605   been evaluated by IARC or US EPA.

1606   Alteration of estrus cycle is the most sensitive effect observed in the various rat studies.
1607   Absorption and retention of Mo is markedly influenced by interactions with dietary Cu
1608   and sulfate and the typical symptoms from excessive Mo intake were similar to those of
1609   copper deficiency including weight loss, growth retardation, anorexia, anemia, diarrhea,
1610   achromotrichia, testicular degeneration, poor conception, deficient lactation, dyspnea,
1611   incoordination and irritation of mucous membranes (Engel *et al*. 1956).

1612   **PDE – Oral Exposure**

1613   Fungwe *et al*. (1990) examined the effects on fertility and reproductive performance of
1614   sodium molybdenate in female rats given drinking water containing 0, 5, 10, 50 or 100
1615   mg Mo/L. After 6 weeks the effect of Mo on the estrous cycle (3 cycles) and vaginal
1616   cytology was determined, and some animals then mated to untreated males. Pregnant
1617   dams continued to be dosed to day 21 of gestation with Mo and fetal effects determined.
1618   Effects on the estrous cycle, gestational weight gain, and the fetus were observed at 10
1619   mg/L and higher; thus, a dose level of 5 mg/L can be considered a NOAEL. Vyskocil and
1620   Viau (1999) calculated this NOAEL to be 0.9 mg Mo/kg/day.

1621   Using modifying factors (F1-F5 as discussed in Appendix 1) the oral PDE is:

1622   PDE = 0.9 mg/kg/day x 50 kg / 5 x 10 x 1 x 5 x 1 = 0.180 mg/day = 180 µg/day.

1623   F4 was selected to be 5 based on the presence of fetal effects.

PDE – Parenteral Exposure

In Vyskocil and Viau (1999), it was reported that oral bioavailability in humans ranged from 28-77%. Turnland *et al.* (2005) report that molybdenum absorption was about 90% in healthy men. Therefore, the parenteral PDE is the same as the oral PDE.

PDE= 180 µg/day.

PDE – Inhalation Exposure

Chronic inflammation in the alveoli was seen in rat and mouse. In addition, a slight trend for bronchiolar alveolar adenoma and carcinoma was observed in male rats exposed to molybdenum trioxide in a 2-year inhalation study (NTP, 1997). Lung neoplasms were not seen in female rats. In mice, bronchiolar alveolar adenoma and carcinoma were observed at the lowest dose of 10 mg/m^3 (6.7 mg/m^3 of Mo).

The inhalation PDE was calculated based on the low dose in the mouse carcinogenicity study, where findings of alveolar and bronchiolar carcinoma were observed, using the modifying factors (F1-F5 as discussed in Appendix 1).

6.7 mg/m^3 ÷1000 m^3/L = 0.0067 mg/L

For continuous dosing = $\frac{0.0067 \text{ mg/L x 6 hr x 5 d}}{24 \text{ hr x 7 d}}$ = 0.0012 mg/L

Daily dose = $\frac{0.0012 \text{ mg/L x 43 L/d}}{0.028 \text{ kg}}$ = 1.83mg/kg

PDE = $\frac{1.83 \text{ mg/kg x 50 kg}}{12 \times 10 \times 1 \times 10 \times 10}$ = 7.6 µg/day.

REFERENCES

Abumrad NN, Schneider AJ, Steel D, Rogers LS. Amino acid intolerance during prolonged total parenteral nutrition reversed by molybdate therapy. Am J Clin Nutr 1981;34(11):2551-9.

Engel RW, Miller RF, Price NO. Added dietary inorganic sulfate and its effect upon rats fed molybdenum. J Nutr 1956;60(4):539-47.

Fundwe TV, Buddingh F, Demick DS, Lox CD, Yang MT, Yang SP. The role of dietary molybdenum on estrous activity, fertility, reproduction and molybdenum and copper enzyme activities of female rats. Nutr Res 1990;10:515-24.

NTP. Toxicology and carcinogenesis studies of molybdenum trioxide (CAS No. 1313-27-5) in F344 rats and B6C3F1 mice (inhalation studies). National Toxicology Program, Public Health Service, U.S. Department of Health and Human Services. 1997.

Turnland JR, Keyes WR, Peiffer GL. Molybdenum absorption, excretion, and retention studied with stable isotopes in young men at five intakes of dietary molybdenum. Am J of Clin Nutr 1995;62:790-6.

Vyskocil A, Viau C. Assessment of molybdenum toxicity in humans. J Appl Toxicol. 1999;19:185-92.

1664 **NICKEL**

1665 **Summary of PDE for Nickel**

Nickel (Ni)			
	Oral	Parenteral	Inhalation
PDE (µg/day)	600	60	6.0

1666 **Introduction**

1667 Nickel (Ni) is a Group 10 element of the first transition series. Although Ni may have
1668 valences of 0, I, II and III, its main oxidation state is +2. Ni is a naturally occurring
1669 metal existing in various mineral forms. In general, the more soluble Ni compounds,
1670 including Ni chloride, Ni sulfate, and Ni nitrate, tend to be more toxic than less soluble
1671 forms, such as Ni oxide and Ni subsulfide. Ni is nutritionally not essential for humans,
1672 but Ni deficiency may cause adverse effects in animals. Nickel as Ni-Al alloys is being
1673 used as catalyst in hydrogenation reactions.

1674 **Safety Limiting Toxicity**

1675 Nickel is genotoxic, but not mutagenic (IARC 2012). There is no indication of
1676 carcinogenicity of Ni salts after oral administration. Depending on the type of salt there
1677 was an increase in tumors in some rodent inhalation studies (ATSDR, 2005; EU EFSA,
1678 2005). Combining all forms of Ni, IARC (2012) classified Ni as a human carcinogen
1679 (Group 1).

1680 In humans and animals, ingestion of large amounts of Ni may cause stomach pain,
1681 depression of body weight and adverse effects on blood and kidneys. Humans generally
1682 become sensitised to Ni after prolonged contact with the skin. Chronic inhalation may
1683 produce adverse changes in lung and nasal cavity in both humans and animals.

1684 **PDE – Oral Exposure**

1685 Human sensitisation to Ni was used to establish the oral PDE, because it is the most
1686 sensitive endpoint. Human data show that an oral challenge dose of 0.012 mg Ni/kg can
1687 induce dermatitis in nickel-sensitized individuals. Exposure to these nickel
1688 concentrations did not result in dermatitis in non-sensitized individuals (Nielsen 1999).
1689 Similar data were presented for 0.02 mg/kg by ATSDR (2005).

1690 PDE = 0.012 mg/kg/day x 50 kg = 0.60 mg/day = 600 µg/day.

1691 **PDE – Parenteral Exposure**

1692 A human study using a stable nickel isotope estimated that 29–40% of the ingested label
1693 was absorbed (based on fecal excretion data) (Patriarca *et al*. 1997). On the basis of
1694 limited oral bioavailability of Ni and water-soluble Ni compound. Therefore, the oral
1695 PDE is divided by a factor of 10 (as described in Section 3.1).

1696 PDE = 600 µg/day / 10 = 60 µg/day.

1697 **PDE – Inhalation Exposure**

1698 For calculation of the inhalation PDE, a relevant form of Ni was selected from the
1699 available data. In 2 year studies with nickel oxide (the form commonly used in stainless
1700 steel coatings), no tumors were observed in hamsters (Wehner *et al*. 1984) or mice (NTP,
1701 1996), but there was some evidence of carcinogenicity in rats (NTP, 2006) and no
1702 evidence of carcinogenicity with inhalation of metallic nickel (Oller, 2008).

1703 Taking into account the modifying factors (F1-F5 as discussed in Appendix 1), the
1704 inhalation PDE is calculated based on the NOAEL in the rat study of 0.5 mg Ni/m^3/day.

1705 For continuous dosing 0.5 mg/m^3 / 1000L/m^3 = 0.0005 mg/L

1706 0.0005 mg/L x 6 hr x 5 d /24 hr x 7 d = 0.000089 mg/L

1707 Daily dose 0.000089 mg/L x 290 L/d / 0.425 kg = 0.060 mg/kg

1708 PDE = 0.060 mg/kg x 50 kg / 5 x 10 x 1 x 10 x 1 = 6.0 µg/day.

1709 **REFERENCES**

1710 ATSDR. Toxicological profile for nickel. Agency for Toxic Substances and Disease
1711 Registry, Public Health Service, U.S. Department of Health and Human Services,
1712 Atlanta, GA. 2005.

1713 Dunnick JK, Elwell MR, Benson JM, Hobbs CH, Hahn FF, Haly PJ, et al. Lung toxicity
1714 after 13-week inhalation exposure to nickel oxide, nickel subsulfide, or nickel sulfate
1715 hexahydrate in F344/N rats and B6C3F1 mice. Fundam Appl Toxicol 1989;12(3):584-94.

1716 Dunnick JK, Elwell MR, Radovsky AE, Benson JM, Hahn FF, Nikula KJ, et al.
1717 Comparative carcinogenic effects of nickel subsulfide, nickel oxide, or nickel sulfate
1718 hexahydrate chronic exposures in the lung. Cancer Res 1995;55(22):5251-6.

1719 EU EFSA. Opinion of the scientific panel on dietetic products, nutrition and allergies on
1720 a request from the Commission related to the tolerable upper intake level of nickel.
1721 European Food Safety Authority. EFSA Journal 2005;146:1-21.

1722 Goodman JE, Prueitt RL, Thakali S, Oller AR. The nickel ion bioavailability of the
1723 carcinogenic potential of nickel-containing substances in the lung. Crit Rev Toxicol
1724 2011;41:142-74.

1725 Haney JY, McCant DD, Sielken RL, Valdez-Flores C, Grant RL. Development of a unit
1726 risk factor for nickel and inorganic nickel compounds based on an updated
1727 carcinogenicity toxicity assessment. Reg Toxicol Pharmacol 2012;62: 191-201.

1728 Heim KE, Bates HK, Rush RE, Oller AR. Oral carcinogenicity study with nickel sulphate
1729 hexahydrate in Fischer 344 rats. Toxicol Sci 2007;224:126-37.

1730 IARC. Arsenic, metals, fibres, and dusts: a review of human carcinogens. Monographs on
1731 the Evaluation of Carcinogenic Risks to Humans. International Agency for Research on
1732 Cancer, World Health Organization, Lyon. 2012;100C.

1733 Nielsen GD, Søderberg U, Jørgensen PJ, Templeton DM, Rasmussen SN, Andersen KE,
1734 et al. Absorption and retention of nickel from drinking water in relation to food intake
1735 and nickel sensitivity. Toxicol Appl Pharmacol 1999;154:67-75.

1736 NTP. Report on carcinogens. National Toxicology Program, Public Health Service, U.S.
1737 Department of Health and Human Services, Bethesda, MD. 2002.

1738 NTP. Toxicology and carcinogenesis studies of nickel oxide. National Toxicology
1739 Program, U.S. Department of Health and Human Services. 2006;Technical Report Series
1740 No. 451.

1741 Oller AR, Kirkpatrick DT, Radovsky A, Bates HK. Inhalation carcinogenicity study with
1742 nickel metal powder in Wistar rats. Toxicol Appl Pharmacol 2008;233:262-75.

1743 Ottolenghi AD, Haseman JK, Payne WW, Falk HL, MacFarland HN, et al. Inhalation
1744 studies of nickel sulfide in pulmonary carcinogenesis of rats. J Natl Cancer Inst
1745 1974;54:1165-72.

1746   Patriarca M, Lyon TD, Fell GS. Nickel metabolism in humans investigated with an oral
1747   stable isotope. Am J Clin Nutr 1997;66:616-21.

1748   Wehner AP, Dagle GE, Busch RH.   Pathogenicity of inhaled nickel compounds in
1749   hamsters. IARC Sci Publ 1984;(53):143-51.

1750 **PALLADIUM**

1751 **Summary of PDE for Palladium**

Palladium (Pd)			
	Oral	Parenteral	Inhalation
PDE (µg/day)	100	10	1.0

1752 **Introduction**

1753 Palladium (Pd) is a steel-white, ductile metallic element resembling and occurring with
1754 the other platinum group metals and nickel. It exists in three states: Pd^0 (metallic), Pd^{2+}
1755 and Pd^{4+}. It can form organometallic compounds, only few of which have found industrial
1756 uses. Palladium (on various supports) is being used as catalyst in hydrogenation
1757 reactions. Palladium metal is stable in air and resistant to attack by most reagents
1758 except aqua regia and nitric acid.

1759 Several mutagenicity tests of different palladium compounds with bacterial or
1760 mammalian cells (Ames test with *Salmonella typhimurium*; SOS chromotest with
1761 *Escherichia coli*; micronucleus test with human lymphocytes) *in vitro* gave negative
1762 results.

1763 **Safety Limiting Toxicity**

1764 The data was reviewed to identify the safety limiting toxicities based on routes of
1765 administration.

1766 **PDE – Oral Exposure**

1767 A number of long-term animal studies have been conducted exploring the toxicity and
1768 carcinogenicity of palladium salts. However, none to date have been executed in
1769 accordance with current guidelines for toxicological studies. The available data suggest
1770 potential NOAELs for palladium in the range of 0.8 – 1.5 mg/kg. A lifetime study with
1771 mice given palladium(II) chloride in drinking-water at a dose of about 1.2 mg Pd/kg/day
1772 found a significantly higher incidence of amyloidosis in several inner organs of males and
1773 females and suppressed growth in males, but not in females (Schroeder and Mitchner,
1774 1971; IPCS, 2002). This study also contained a signal that suggested a possible
1775 carcinogenic endpoint; however, the design of the study (single dose level, pooling of the
1776 tumor rates from male and female animals, and a significant increase in the age of the
1777 treated *vs* control animals) limited the utility of the data to assess the carcinogenic
1778 potential.

1779 Taking into account the modifying factors (F1-F5 as discussed in Appendix 1), the oral
1780 PDE is calculated based on the LOEL of 1.2 mg/kg/day.

1781 PDE = 1.2 mg/kg/day x 50 kg / 12 x 10 x 1 x 5x 1 = 0.1 mg/day = 100 µg/day.

1782 **PDE – Parenteral Exposure**

1783 The safety review for Pd was unable to identify any significant assessments upon which
1784 to calculate a PDE for parenteral routes of exposure. Palladium(II) chloride ($PdCl_2$) was
1785 poorly absorbed from the digestive tract (<0.5% of the initial oral dose in adult rats or
1786 about 5% in suckling rats after 3-4 days). Absorption/retention in adult rats was higher
1787 following intratracheal or intravenous exposure, resulting in total body burdens of 5% or
1788 20%, respectively, of the dose administered, 40 days after dosing (IPCS, 2002). On the
1789 basis of an oral bioavailability the PDE for palladium for parenteral exposure is:

1790   PDE = 100 µg/day / 10 = 10 µg/day.

1791   **PDE – Inhalation Exposure**

1792   There are no adequate inhalation data on Pd. Therefore, the inhalation PDE for
1793   palladium was derived from the oral PDE by division by a factor of 100 (as described in
1794   Section 3.1).

1795   PDE = 100 µg/day / 100 = 1.0 µg/day.

1796   REFERENCES

1797   IPCS. Palladium. Environmental Health Criteria 226. International Programme on
1798   Chemical Safety. World Health Organization, Geneva. 2002.

1799   Schroeder HA, Mitchener M. Scandium, chromium (VI), gallium, yttrium, rhodium,
1800   palladium, indium in mice: Effects on growth and life span. J Nutr 1971;101:1431-8.

1801 **PLATINUM**

1802 **Summary of PDE for Platinum**

Platinum (Pt)			
	Oral	Parenteral	Inhalation
PDE (µg/day)	1000	10	1.4

1803 **Introduction**

1804 Platinum (Pt) is a Group VIII element of the third transition series. It is the most
1805 important of the six heaviest of the group VIII elements, collectively called the "platinum
1806 group metals" or "platinoids", including palladium, osmium, rhodium, ruthenium and
1807 iridium. Platinum and Pd are more chemically reactive than the other platinoids.
1808 Metallic Pt has been shown to catalyze many oxidation-reduction and decomposition
1809 reactions and the major industrial use of Pt is as a catalyst. Pt complexes exhibiting a
1810 range of oxidation states are known, although the principal valences are Pt II and IV. Pt
1811 II forms a tetra-coordinate aqua ion $[Pt (H_2O)_4]^{2+}$. The most common Pt IV catalysts are
1812 chloroplatinate salts such as tetra and hexachloroplatinate ions.

1813 **Safety Limiting Toxicity**

1814 The data was reviewed to identify the safety limiting toxicities based on routes of
1815 administration.

1816 Chlorinated salts of platinum are responsible for platinum related hypersensitivity and
1817 are a major occupational health concern (US EPA, 2009). The hypersensitivity appears to
1818 be the most sensitive endpoint of chloroplatinate exposure, at least by the inhalation
1819 route. Signs include urticaria, contact dermatitis of the skin, and respiratory disorders
1820 ranging from sneezing, shortness of breath, and cyanosis to severe asthma (IPCS, 1991).
1821 Exposure reduction was effective in resolving symptoms (Merget *et al.* 2001). Neutral
1822 complexes and complexes without halogenated ligands do not appear allergenic (US EPA,
1823 2009; EU SCOEL, 2011). The risk of hypersensitivity appears to be related to sensitizing
1824 dose and dose and length of exposure (IPCS, 1991; US EPA, 2009; Arts *et al.* 2006) and
1825 cigarette smoking (US EPA, 2009; Merget *et al.* 2000; Caverley, 1995).

1826 **PDE – Oral Exposure**

1827 No experimental data are available on the carcinogenicity of platinum and platinum
1828 compounds, and toxicology data are limited (US EPA, 2009). In one study in male rats
1829 administered $PtCl_2$ (relatively insoluble) and $PtCl_4$ (soluble) for 4 weeks, the toxicity of
1830 the two platinum salts was investigated. No significant effects on body weight gain or
1831 food consumption for either compound, and no effects were observed on hematological
1832 parameters for $PtCl_2$. Some hematological parameters were influenced by $PtCl_4$; a
1833 reduction of about 13% in hematocrit and erythrocyte parameters was reported at the
1834 dose of 50 mg Pt/kg in the diet. Platinum concentration increased in tissues in animals
1835 dosed with either compound, particularly the kidney. For this reason plasma creatinine
1836 was examined, and found to be increased in animals dosed with $PtCl_4$ when added in the
1837 diet at 50 mg Pt/kg diet for 4 weeks, but not $PtCl_2$. This dose corresponded to 21 mg
1838 Pt/animal (Reichlmayr-Lais *et al.* 1992). This study was used in the determination of the
1839 PDE as one endpoint in the study was renal toxicity (plasma creatinine), a target organ
1840 of platinum and a site of accumulation. Renal toxicity is an also an adverse effect of
1841 treatment with chemotherapeutic agents such as cisplatin.
1842 Taking into account the modifying factors (F1-F5 as discussed in Appendix 1), the oral
1843 PDE is calculated based on the NOAEL of 10 mg/kg/day.

1844   PDE = 10 mg/kg/day x 50 kg / 5 x 10 x 10 x 1 x 1 = 1 mg/day = 1000 µg/day.

1845   **PDE – Parenteral Exposure**

1846   The safety review for platinum identified limited assessments of platinum salt toxicity
1847   for parenteral routes of administration. The oral absorption of platinum salts is very low
1848   (<1%) (US EPA, 2009). Therefore, the oral PDE is divided by a factor of 100 (as described
1849   in section 3.1).

1850   PDE = 1000 µg/day / 100 = 10 µg/day.

1851   **PDE – Inhalation Exposure**

1852   Due to the use of the chloroplatinates in catalytic converters, numerous animal (Biagini
1853   *et al.* 1983) and human (Pepys *et al.* 1972; Pickering 1972; Merget *et al.* 2000; Cristaudo
1854   *et al.* 2007) studies have been conducted. The US EPA (1977; 2009) and the EU SCOEL
1855   (2011) have also examined the safety of chloroplatinates based on sensitization. The EU
1856   SCOEL concluded that the database does not allow for setting an occupational limit for
1857   soluble platinum salts. The US DoL (2013) has established an occupational limit for
1858   soluble Pt salts at 2 µg/m^3; however, whether this exposure level is completely protective
1859   of workers has been questioned (Merget and Rosner, 2001).

1860   Taking into account the modifying factors (F1-F5 as discussed in Appendix 1), the
1861   inhalation PDE is calculated as:

1862   2 µg/m^3 ÷1000 m^3/L = 0.002 µg/L

1863   For continuous dosing = 0.002 µg/<u>L x 8 hr x 5</u> d = 0.00048 µg/L
1864   24 hr x 7 d

1865   Daily dose =<u> 0.00048 µg/L x 28800L/d</u> = 0.27 µg/kg/d
1866   50 kg

1867   PDE <u>= 0.27 µg/kg/d x 50 kg</u> = 1.37 µg/day ~1.4 µg/day.
1868   1 x 10 x 1 x 1 x 1

1869   **REFERENCES**

1870   Arts JHE, Mommers C, de Heer C. Dose-response relationships and threshold levels in
1871   skin and respiratory allergy. Crit Rev Toxicol 2006; 36:219-51.

1872   Biagini RE, Moorman WJ, Smith RJ, Lewis TR, Bernstein IL. Pulmonary
1873   hyperreactivity in cynomolgus monkeys (Macaca fasicularis) from nose-only inhalation
1874   exposure to disodium hexachloroplatinate, Na$_2$PtCl$_6$. Toxicol Appl Pharmacol
1875   1983;69:377-84.

1876   Caverley AE, Rees D, Dowdeswell RJ, Linnett PJ, Kielkowski D. Platinum salt
1877   sensitivity in refinery workers: incidence and effects of smoking and exposure. Int J
1878   Occup Environ Med 1995;52:661-66.

1879   Cristaudo A, Picardo M, Petrucci F, Forte G, Violante N, Senofonte O, Alimonti A.
1880   Clinical and allergological biomonitoring of occupational hypersensitivity to platinum
1881   group elements. Anal Lett 2007;40:3343-59.

1882   EU SCOEL. Recommendation from the scientific committee on occupational exposure
1883   limits for platinum and platinum compounds. European Union Scientific Committee on
1884   Occupational Exposure Limits. 2011;SCOEL/SUM/150.

1885   IPCS. Platinum. Environmental Health Criteria 125. International Programme on
1886   Chemical Safety. World Health Organization, Geneva. 1991.

Merget R; Kulzer R; Dierkes-Globisch A, Breitstadt R, Gebler A, Kniffka A, Artelt S, Koenig HP, Alt F, Vormberg R, Baur X, Schultze-Werninghaus G. Exposure-effect relationship of platinum salt allergy in a catalyst production plant: conclusions from a 5-year prospective cohort study. J Allergy Clin Immunol 2000;105:364-370.

Merget R, Caspari C, Kulzer SA, Dierkes-Globisch R, Kniffka A, Degens P, et al. Effectiveness of a medical surveillance program for the prevention of occupational asthma caused by platinum salts: a nested case control study. J Allergy Clin Immunol 2001;107:707-12.

Merget R, Rosner G. Evaluation of the health risk of platinum group metals emitted from automative catalytic converters. Sci Total Environ 2001;270:165-73.

Pepys J, Pickering CAC, Hughes EG. Asthma due to inhaled chemical agents--complex salts of platinum. Clin Exp Allergy 1972;2:391-96.

Pickering CAC. Inhalation tests with chemical allergens: complex salts of platinum. Proc R Soc Med 1972;65:2-4.

Reichlmayr-Lais AM, Kirchgessner M, Bader R. Dose-response relationships of alimentary $PtCl_2$ and $PtCl_4$ in growing rats. J Trace Elem Electrolytes Health Dis 1992;6(3):183-7.

US DoL (OHSA). 29 CRF 1910.1000 Table Z-1. Limits for air contaminants. U.S. Department of Labor. 2013.

US EPA. Platinum-group metals. Environmental Health Effects Research Series 1977;EPA-600/1-77-040.

US EPA. Toxicological review of halogenated platinum salts and platinum compounds. Integrated Risk Information System (IRIS). 2009.

US EPA. Toxicological review of halogenated platinum salts and platinum compounds. In support of summary information on the Integrated Risk Information System (IRIS). 2009.

1914   **SELENIUM**

1915   **Summary of PDE for Selenium**

Selenium (Se)			
	Oral	Parenteral	Inhalation
PDE (µg/day)	170	85	140

1916   **Introduction**

1917   Selenium is present in the earth's crust, often in association with sulfur-containing
1918   minerals. It can assume four oxidation states (-2, 0, +4, +6) and occurs in many forms,
1919   including elemental selenium, selenites and selenates. Selenium is an essential trace
1920   element for many species, including humans. Selenium is incorporated into proteins *via*
1921   a specific selenocysteine tRNA. Selenium is being used as a catalyst in the manufacture
1922   of rubber. Ru-Se catalysts are used in oxygen reduction. Aryl- and alkyl-Selenium
1923   reagents have various applications in organic synthesis.

1924   **Safety Limiting Toxicity**

1925   Selenium was listed as a Group 3 compound by IARC (1987), not classifiable for
1926   carcinogenesis. The only selenium compound that has been shown to be carcinogenic in
1927   animals is selenium sulfide (NTP, 1980). According to the US EPA, selenium sulfide is
1928   in Group B2 (probable human carcinogen) (US EPA, 2002). Other selenium compounds
1929   are classified as D; not classifiable as to carcinogenicity in humans.

1930   The most significant toxicity observed in these assessments was hepatotoxicity.

1931   **PDE – Oral Exposure**

1932   In a rat carcinogenicity study of selenium sulfide, the NOAEL for hepatocellular carcinoma
1933   was 3 mg/kg/day (1.7 mg Se/kg/day) (NTP, 1980). There is insufficient data to assess
1934   carcinogenicity of other forms of selenium, and the human relevance of the rodent liver
1935   tumors has been questioned (IARC, 1999). Some human data are available but only in a
1936   limited number of subjects (ATSDR, 2003). The PDE is in line with the MRL of 5
1937   µg/kg/day for Se (ATSDR 2003).

1938   Taking into account the modifying factors (F1-F5 as discussed in Appendix 1), the oral
1939   PDE is calculated as below.

1940   PDE = 1.7 mg/kg/day x 50 kg / 5 x 10 x 1 x 10 x 1 = 170 µg/day.

1941   **PDE – Parenteral Exposure**

1942   The safety review for selenium was unable to identify any significant assessments upon
1943   which to calculate a PDE for parenteral routes of exposure. Studies in humans and
1944   experimental animals indicate that, when ingested, several selenium compounds
1945   including selenite, selenate, and selenomethionine are readily absorbed, often to greater
1946   than 80% of the administered dose (ATSDR, 2003). On the basis of oral bioavailability of
1947   ~80%, the PDE for selenium for parenteral exposure is (as described in section 3.1).

1948   PDE = 170 µg/day / 2 = 85 µg/day.

1949 **PDE – Inhalation Exposure**

1950 The safety review for selenium was unable to identify any significant animal models or
1951 clinical studies of inhalation toxicity. However, occupational limits have established
1952 time weighted averages for selenium exposures of 0.2 mg/m³ (US DoL, 2013).

1953 Taking into account the modifying factors (F1-F5 as discussed in Appendix 1), the
1954 inhalation PDE is calculated as below.

1955 0.2 mg/m³ /1000 L/m³= 0.0002 mg/L

1956 For continuous dosing = 0.0002 mg/L x 8 h x 5 d/24 x 7 = 0.0000476 mg/L

1957 Daily dose = 0.0000476 mg/L x 28800 L/50 kg = 0.027 mg/kg

1958 PDE = $\underline{0.027 \text{ mg/kg x 50 kg}}$ = 0.135 mg/day = 140 µg/day.
1959   1 x 10 x 1 x 1 x 1

1960 REFERENCES

1961 ATSDR. Toxicological profile for selenium. Agency for Toxic Substances and Disease
1962 Registry, Public Health Service, U.S. Department of Health and Human Services,
1963 Atlanta, GA. 2003.

1964 IARC. Overall evaluations of carcinogenicity: An update of IARC monographs volumes 1
1965 to 42. Monographs on the Evaluation of the Carcinogenic Risks to Humans. International
1966 Agency for Research on Cancer, World Health Organization, Lyon.1987;Suppl 7.

1967 IARC. Some aziridines, N-, S- and O-mustards and selenium. Summary of data reported
1968 and evaluation. Monographs on the Evaluation of Carcinogenic Risks to Humans.
1969 International Agency for Research on Cancer, World Health Organization, Lyon. 1999.

1970 NTP. Bioassay of selenium sulfide (gavage) for possible carcinogenicity. National
1971 Toxicology Program, US Department of Health and Human Services. 1980;Technical
1972 Report Series No 194.

1973 US DoL (OHSA). 29 CRF 1910.1000 Table Z-1. Limits for air contaminants. U.S.
1974 Department of Labor. 2013.

1975 US EPA. Selenium and compounds (CAS No. 7782-49-2). Integrated Risk Information
1976 System (IRIS). 2002.

1977 **SILVER**

1978 **Summary of PDE for Silver**

Silver (Ag)			
	Oral	Parenteral	Inhalation
PDE (µg/day)	170	35	6.9

1979 **Introduction**

1980 Silver (Ag) is present in silver compounds primarily in the oxidation state +1 and less
1981 frequently in the oxidation state +2. Ag occurs naturally mainly in the form of very
1982 insoluble and immobile oxides, sulfides and some salts. The most important silver
1983 compounds in drinking-water are silver nitrate and silver chloride. Most foods contain
1984 traces of silver in the 10–100 µg/kg range. Ag is nutritionally not essential and no
1985 metabolic function is known. Silver is being used as a catalyst in the oxidation of
1986 ethylene to ethyleneoxide. Silver-Cadmium alloy is used in selective hydrogenation of
1987 unsaturated carbonyl compounds. Silver oxide is used as a mild oxidizing agent in
1988 organic synthesis.

1989 **Safety Limiting Toxicity**

1990 Silver is not mutagenic. Animal toxicity studies and human occupational studies have
1991 not provided sufficient evidence of carcinogenicity. Based on these data Ag is not
1992 expected to be carcinogenic in humans (ATSDR, 1990).

1993 Argyria appears to be the most sensitive clinical effect in response to human Ag intake.
1994 Silver acetate lozenges are used in smoking cessation (Hymowitz and Eckholdt, 1996).
1995 Argyria, a permanent bluish-gray discoloration of the skin, results from the deposition of
1996 Ag in the dermis combined with an Ag-induced production of melanin. Inhalation of high
1997 levels of silver can result in lung and throat irritation and stomach pains (ATSDR, 1990).

1998 **PDE – Oral Exposure**

1999 Silver nitrate was added at 0.015% to the drinking water of female mice (0.9 g/mouse;
2000 32.14 mg/kg silver nitrate; 64% silver) for 125 days to examine neurobehavioral activity
2001 of the animals based on potential neurotoxicity of silver (Rungby and Danscher, 1984).
2002 Treated animals were hypoactive relative to controls; other clinical signs were not noted.
2003 In a separate study, silver was shown to be present in the brain after mice were injected
2004 with 1 mg/kg ip silver lactate (Rungby and Danscher, 1983). The oral PDE is in line with
2005 the reference dose of 5 µg/kg/day (US EPA, 2003).

2006 Taking into account the modifying factors (F1-F5 as discussed in Appendix 1), the oral
2007 PDE is calculated as below.

2008 20 mg/kg x 50 kg / 12 x 10 x 5 x1 x 10 = 167 µg/d ~170 µg/day.

2009 A factor 10 was chosen for F5 as a NOAEL was not seen in this study and few
2010 toxicological endpoints were examined.

2011 **PDE – Parenteral Exposure**

2012 US EPA (2003) identified a LOAEL of 0.014 mg/kg Ag/d using long-term (2 to 9 years)
2013 human iv data based on argyria following colloidal and organic silver medication.

2014 Taking into account the modifying factors (F1-F5 as discussed in Appendix 1), the
2015 parenteral PDE is calculated as below.

2016 0.014 mg/kg/d x 50 kg = 700 ug/d/1 x 10 x 1 x 1 x 2 = 35 µg/day.

2017 A factor of 2 was chosen for F5 as the finding of argyria was not considered a serious
2018 toxicity and a factor of 10 is used for F2, for a combined modifying factor of 20.

PDE – Inhalation Exposure

2020 Lung and throat irritation and stomach pains were the principal effects in humans after
2021 inhalation of high Ag levels.

2022 Using the TLV of 0.01 mg/m³ for silver metal and soluble compounds (US DoL, 2013),
2023 taking into account the modifying factors (F1-F5 as discussed in Appendix 1), the
2024 inhalation PDE is calculated as:

2025 0.01 mg/m³ /1000 L/m³= 0.00001 mg/L

2026 For continuous dosing = 0.00001 mg/L x 8 h x 5 d/24 x 7 = 0.00000238 mg/L

2027 Daily dose = $\underline{0.00000238 \text{ mg/L} \times 28800 \text{ L/day}}$ = 0.00137 mg/kg/day
2028   50 kg

2029 PDE = $\underline{0.00137 \text{ mg/kg} \times 50 \text{ kg}}$ = 0.0069 mg/day = 6.9 µg/day.
2030   1 x 10 x 1 x 1 x 1

2031 The factor F2 was set to 10 to extrapolate to the general population.

REFERENCES

2033 ATSDR. Toxicological Profile for Silver. Agency for Toxic Substances and Disease
2034 Registry, Public Health Service, U.S. Department of Health and Human Services,
2035 Atlanta, GA. 1990.

2036 Hymowitz N, Eckholt H. Effects of a 2.5-mg silver acetate lozenge on initial and long-
2037 term smoking cessation. Prev Med 1996;25:537-46.

2038 Rungby J, Danscher G. Hypoactivity in silver exposed mice. Acta Pharmacol Toxicol
2039 1984;55:398-401.

2040 Rungby J, Danscher G. Localization of exogenous silver in brain and spinal cord of silver
2041 exposed rats. Acta Neuropathol 1983;(60)1-2:92-98.

2042 US DoL (OHSA). 29 CRF 1910.1000 Table Z-1. Limits for air contaminants. U.S.
2043 Department of Labor. 2013.

2044 US EPA. Silver (CASRN 7440-22-4). Integrated Risk Information System (IRIS). 2003.

2045   **THALLIUM**

2046   **Summary of PDE for Thallium**

Thallium (Tl)			
	Oral	Parenteral	Inhalation
PDE (µg/day)	8.0	8.0	69

2047   **Introduction**

2048   Pure thallium (Tl) is a bluish-white metal. It exists primarily in two valence states:
2049   monovalent (thallous) and trivalent (thallic). Monovalent thallium is similar to
2050   potassium (K+) in ionic radius and electrical charge, which contribute to its toxic nature.
2051   Many of the thallium salts are soluble in water with the exception of the insoluble
2052   thallium (III) oxide. Tl sulfate has been used in medicine, primarily as a depilatory agent,
2053   but also to treat infections, such as venereal diseases, ringworm of the scalp, typhus,
2054   tuberculosis, and malaria. Thallium(III) salts are being used in organic synthesis. Tl is
2055   nutritionally not essential and no metabolic function is known (ATSDR, 1992).

2056   **Safety Limiting Toxicity**

2057   In humans and animals, the skin, especially the hair follicles, appears to be the most
2058   sensitive target of toxicity from repeated oral exposure to Tl (US EPA, 2009).

2059   **PDE – Oral Exposure**

2060   The primary target organ for oral exposure to Tl in humans and animals appears to be
2061   the skin, especially the hair follicles, as shown in a 90-day toxicity rat study with Tl
2062   sulfate. The NOAEL was defined at 0.04 mg Tl/kg on the basis of an increased incidence
2063   of alopecia at the higher doses (Stoltz *et al.* 1986; US EPA, 2009). Thus, the oral PDE
2064   was determined on the basis of the NOAEL of 0.04 mg Tl/kg in rat.

2065   Taking into account the modifying factors (F1-F5 as discussed in Appendix 1), the oral
2066   PDE is calculated as below.

2067   PDE = 0.04 mg/kg/day x 50 kg / 5 x 10 x 5 x 1 x 1 = 0.008 mg/day = 8.0 µg/day.

2068   **PDE – Parenteral Exposure**

2069   No relevant data on parenteral exposure to thallium compounds were found. The
2070   bioavailability of soluble thallium salts is high (> 80%) (US EPA, 2009). Therefore, the
2071   parenteral PDE is the same as the oral PDE.

2072   PDE = 8.0 µg/day.

2073   **PDE – Inhalation Exposure**

2074   No relevant data on inhalation exposure to thallium compounds were found. Using the
2075   TLV of 0.1 mg/m^3 for thallium, soluble compounds (US DoL, 2013; CEC, 2000).

2076   Taking into account the modifying factors (F1-F5 as discussed in Appendix 1), the
2077   inhalation PDE is calculated as:

2078   0.1 mg/m^3 /1000 L/m^3= 0.0001 mg/L

2079   For continuous dosing = 0.0001 mg/L x 8 h x 5 d/24 x 7 = 0.0000238 mg/L

2080

2081   Daily dose = 0.0000238 mg/L x 28800 L/day = 0.0137 mg/kg/day

2082   50 kg

2083   PDE =   <u>0.0137 mg/kg x 50 kg</u>   = 0.069 mg/day = 69 µg/day.

2084   1 x 10 x 1 x 1 x 1

2085   **REFERENCES**

2086   ATSDR. Toxicological profile for thallium. Agency for Toxic Substances and Disease
2087   Registry, Public Health Service, U.S. Department of Health and Human Services,
2088   Atlanta, GA. 1992.

2089   CEC. Commission of the European Communities. Commission Directive 2000/39/EC of 8
2090   June 2000 establishing a first list of indicative occupational exposure limit values in
2091   implementation of Council Directive 98/24/EC on the protection of the health and safety
2092   of workers from the risks related to chemical agents at work. Official Journal of the
2093   European Communities 2000;L142 (16/06/2000):47-50.

2094   Stoltz ML, Stedham MA, Brown LK, et al. Subchronic (90-day) toxicity of thallium (I)
2095   sulfate (CAS No. 7446-18-6) in Sprague-Dawley rats. Final Report. Project no. 8702-
2096   L(18). 1980. Prepared for U.S. Environmental Protection Agency by Midwest Research
2097   Institute; cited in: OEHHA. Public health goal for thallium in drinking water. Office of
2098   Environmental Health Hazard Assessment, Berkeley and Sacramento, CA. 1999

2099   US DoL (OHSA). 29 CRF 1910.1000 Table Z-1. Limits for air contaminants. U.S.
2100   Department of Labor. 2013.

2101   US EPA. Toxicological review of thallium and compounds (CAS No. 7440-28-0). Integrated
2102   Risk Information System (IRIS). 2009.

2103 **TIN**

2104 **Summary of PDE for Tin**

Tin (Sn)			
	Oral	Parenteral	Inhalation
PDE (µg/day)	6400	640	64

2105 **Introduction**

2106 Tin (Sn) is a silvery-white metal that exists in valence states of 2 and 4. The most
2107 important inorganic compounds of tin are its oxides, chlorides, fluorides and halogenated
2108 sodium stannates and stannites. Tin is present in some multi-vitamin and mineral food
2109 supplements (levels up to 10 µg Sn/tablet). Tin is possibly nutritionally essential for
2110 some animals, it has not been shown to be essential for humans. Tin(II) chloride is being
2111 used as a reducing agent, and as a stabilizer of polyvinylchloride (PVC). This safety
2112 assessment focuses on inorganic tin considering that the more frequent occurrence of
2113 inorganic tin is more relevant with respect to metal impurities in drug products than
2114 organic tin compounds.

2115 **Safety Limiting Toxicity**

2116 There is no indication of *in vivo* genotoxicity or carcinogenicity for tin and tin salts. In
2117 several studies in rats, a decrease in hemoglobin as an early sign for anemia, was the
2118 most sensitive endpoint.

2119 **PDE – Oral Exposure**

2120 Anemia was the most sensitive endpoint in rats after repeated oral administration. Thus,
2121 the PDE for oral exposure was determined on the basis of the lowest NOAEL, i.e., 150
2122 ppm (equivalent to 32 mg Sn/kg/day). This value was obtained from a 90-day study in
2123 rats based on signs of anemia starting at 500 ppm in rats exposed to stannous chloride
2124 *via* diet (De Groot *et al*. 1973).

2125 Taking into account the modifying factors (F1-F5 as discussed in Appendix 1), the oral
2126 PDE is calculated as below.

2127 PDE = 32 mg/kg/day x 50 kg / 5 x 10 x 5 x 1 x 1 = 6.4 mg/day = 6400 µg/day.

2128 **PDE – Parenteral Exposure**

2129 The safety review for tin was unable to identify any significant assessments upon which
2130 to calculate a PDE for parenteral routes of exposure. On the basis of an oral
2131 bioavailability of about 5% for tin and inorganic tin compounds (ATSDR, 2005), and
2132 using the default factor of 10, the PDE for tin for a parenteral exposure is (as described
2133 in Section 3.1).

2134 PDE = 6400 µg/day / 10 = 640 µg/day.

2135 **PDE – Inhalation Exposure**

2136 The safety review for tin was unable to identify any significant assessments on inorganic
2137 tin upon which to calculate a PDE for inhalation routes of exposure. Although a TLV is
2138 available for tin (2 mg/m[3;] US DoL, 2013), there is insufficient data to set a MRL (ATSDR
2139 2005; EU SCOEL 2003).

2140 Therefore, the PDE for tin is calculated by using a factor of 100 to convert the oral PDE
2141 to the inhalation PDE (as described in Section 3.1).

2142 PDE = 6400 µg/day / 100 = 64 µg/day.

2143 **REFERENCES**

2144 ATSDR. Toxicological profile for tin and tin compounds. Agency for Toxic Substances and
2145 Disease Registry, Public Health Service, U.S. Department of Health and Human
2146 Services, Atlanta, GA. 2005.

2147 De Groot AP, Feron V, Til H. Short-term toxicity studies on some salts and oxides of tin
2148 in rats. Food Cos and Toxicol 1972;11:19-30.

2149 EU SCOEL. Recommendation from the scientific committee on occupational exposure
2150 limits for tin and inorganic tin compounds. European Union Scientific Committee on
2151 Occupational Exposure Limits. 2003;SCOEL/SUM/97.

2152 US DoL (OHSA). 29 CRF 1910.1000 Table Z-1. Limits for air contaminants. U.S.
2153 Department of Labor. 2013.

2154 **VANADIUM**

2155 **Summary of PDE for Vanadium**

Vanadium (V)			
	Oral	Parenteral	Inhalation
PDE (µg/day)	120	12	1.2

2156 **Introduction**

2157 Vanadium (V) is present as a trace element in the earth's crust and can exist in a variety
2158 of oxidation states (-1, 0, +2, +3, +4 and +5). V is also present in trace quantities in most
2159 biological organisms with the principal ions being vanadate, VO_3^- and vanadyl, VO_2^+.
2160 Absorption of vanadium from the gastrointestinal tract is poor.   Estimates of total
2161 dietary intake of vanadium in humans range from 10 to 60 µg/day. Intake from drinking
2162 water depends on the water source and estimates are up to 140 µg/day.   Human
2163 populations have variable serum concentrations of vanadium, with 2 µg/L being the high
2164 end of the normal range. Despite its ubiquitous presence in the body, an essential
2165 biological role for vanadium in humans has not been established. Vanadium has been
2166 reported to have potentially beneficial effects in treatment of osteoporosis, osteopenia,
2167 cancer, and diabetes. Oral vanadyl sulfate in amounts up to 20 mg/day is included in
2168 some dietary supplements intended to promote muscle growth. Vanadium oxide is used
2169 as a catalyst in the manufacturing of sulfuric acid.

2170 **Safety Limiting Toxicity**

2171 Vanadium is genotoxic, but not mutagenic (ATSDR, 2009). Vanadium pentoxide is
2172 classified as a possible human carcinogen (Group 2B; IARC, 2012).

2173 **PDE – Oral Exposure**

2174 Following oral administration to animals and humans the gastrointestinal tract,
2175 cardiovascular, and hematological system are the primary targets of toxicity. The most
2176 appropriate study to assess vanadium toxicity through oral administration was
2177 conducted in humans exposed to vanadium for 12 weeks. In these studies, no significant
2178 alterations in hematological parameters, liver function (as measured by serum enzymes),
2179 cholesterol and triglyceride levels, kidney function (as measured by blood urea nitrogen),
2180 body weight, or blood pressure were observed in subjects administered *via* capsule 0.12
2181 or 0.19 mg vanadium as ammonium vanadyl tartrate or vanadyl sulfate for 6–12 weeks
2182 (ATSDR, 2012). The oral NOAEL of 0.12 mg vanadium/kg/day for hematological and
2183 blood pressure effects was used to calculate the oral PDE.

2184 Taking into account the modifying factors (F1-F5 as discussed in Appendix 1), the oral
2185 PDE is calculated as below.

2186 PDE = 0.12 mg/kg/day x 50 kg / 1 x 10 x 5 x 1 x 1 = 0.12 mg/day = 120 µg/day.

2187 **PDE – Parenteral Exposure**

2188 The safety review for vanadium was unable to identify any significant assessments upon
2189 which to calculate a PDE for parenteral routes of exposure. On the basis of an
2190 approximate oral bioavailability of <1–10% for vanadium and inorganic vanadium
2191 compounds (ATSDR, 2012), the oral PDE was divided by 10 (as described in Section 3.1).

2192 PDE = 120 µg/day / 10 = 12 µg/day.

2193

2194 **PDE – Inhalation Exposure**

2195 A two year chronic inhalation exposure study in rats was considered for use for the
2196 inhalation PDE for vanadium. In this study, carcinogenic effects were observed to the
2197 lowest dose tested, 0.5 mg/m^3 vanadium pentoxide (Ress *et al*. 2003).   Vanadium
2198 pentoxide is a caustic agent and is not considered to be present in drug products.
2199 Therefore, the inhalation PDE for vanadium was derived from the oral PDE by division
2200 by a factor of 100 (as described in Section 3.1).

2201 PDE = 120/100 = 1.2 µg/day.

2202 **REFERENCES**

2203 ATSDR. Toxicological profile for vanadium. Agency for Toxic Substances and Disease
2204 Registry, Public Health Service, U.S. Department of Health and Human Services,
2205 Atlanta, GA. 2012.

2206 IARC. Arsenic, metals, fibres, and dusts: a review of human carcinogens. Monographs on
2207 the Evaluation of Carcinogenic Risks to Humans. International Agency for Research on
2208 Cancer, World Health Organization, Lyon. 2012;100C.

2209 Ress NB, Chou BJ, Renne RA, Dill JA, Miller RA, Roycroft JH, et al. Carcinogenicity of
2210 inhaled vanadium pentoxide in F344/N rats and B6C3F1 mice. Toxicol Sci
2211 2003;74(2):287-96.

2212 **Appendix 4: Illustrative Example – Calculation Options for Converting PDEs**
2213 **to Concentrations**

2214 **Examples for Converting PDEs into Permitted Elemental Impurity**
2215 **Concentrations**

2216 **Option 1:** Permitted common concentration limits of elemental impurities across drug
2217 product component materials for products with daily intakes of not more than 10 grams.

2218 For this example, consider a solid oral drug product with a maximum daily intake of 2.5
2219 grams, containing 9 components (1 drug substance and 8 excipients, see Table A.4.1).
2220 Because this drug product does not exceed a maximum daily intake of 10 grams, the
2221 concentrations in Table A.2.2 may be used. As Option 1 has a common permitted
2222 concentration, each of the 9 components can be used at any level in the formulation. The
2223 drug substance synthesis uses Pd and Ni catalysts, and the applicant is also concerned
2224 about Pb, As, Cd, Hg, and V on the basis of the risk assessment. The maximum daily
2225 intake of each elemental impurity in the drug product is given in Table A.4.2 assuming
2226 that each elemental impurity is present at the concentration given in Table A.2.2. The
2227 maximum potential daily intake of an elemental impurity is determined using the actual
2228 drug product daily intake and the concentration limit for the elemental impurity in Table
2229 A.2.2 (concentration multiplied by the actual daily intake of the drug product of 2.5
2230 grams). The maximum daily intake given for each elemental impurity is not a
2231 summation of values found in the individual columns.

2232 This calculation demonstrates that no elemental impurities exceed their PDEs. Thus if
2233 these concentrations in each component are not exceeded, the drug product is assured to
2234 meet the PDEs for each identified elemental impurity.

2235 **Table A.4.1: Maximum Daily Intake of Components of the Drug Product**

Component	Daily Intake, g
Drug Substance	0.200
MCC	1.100
Lactose	0.450
Ca Phosphate	0.350
Crospovidone	0.265
Mg Stearate	0.035
HPMC	0.060
Titanium Dioxide	0.025
Iron Oxide	0.015
Drug Product	2.500

2236

2237 **Table A.4.2**: **Permitted Concentrations from Table A.2.2 (assuming uniform**
2238 **concentrations and 10 grams daily intake)**

Component	Maximum Permitted Concentration (µg/g)						
	Pb	As	Cd	Hg	Pd	V	Ni
Drug Substance	0.5	1.5	0.5	4	10	12	60
MCC	0.5	1.5	0.5	4	10	12	60
Lactose	0.5	1.5	0.5	4	10	12	60
Ca Phosphate	0.5	1.5	0.5	4	10	12	60
Crospovidone	0.5	1.5	0.5	4	10	12	60
Mg Stearate	0.5	1.5	0.5	4	10	12	60
HPMC	0.5	1.5	0.5	4	10	12	60
Titanium Dioxide	0.5	1.5	0.5	4	10	12	60
Iron Oxide	0.5	1.5	0.5	4	10	12	60
Maximum Daily intake, µg	**1.25**	**3.75**	**1.25**	**10**	**25**	**30**	**150**
PDE, µg/day	**5.0**	**15**	**5.0**	**40**	**100**	**120**	**600**

2239
2240 **Option 2a:** Permitted common concentration limits across drug product component
2241 materials for a product with a specified daily intake:

2242 For this example, consider the same solid oral drug product with a maximum daily
2243 intake of 2.5 grams, containing 9 components (1 drug substance and 8 excipients, see
2244 Table A.4.1) used in Option 1. As Option 2a has a common permitted concentration,
2245 each of the 9 components can be used at any level in the formulation. The drug
2246 substance synthesis uses Pd and Ni catalysts, and the applicant is also concerned about
2247 Pb, As, Cd, Hg, and V on the basis of the risk assessment. The concentration of each
2248 elemental impurity identified in the risk assessment can be calculated using the PDEs in
2249 Table A.2.1 and equation 1.

2250 The maximum potential daily intake of an elemental impurity is determined using the
2251 actual drug product daily intake and the concentration limit for the elemental impurity
2252 in Table A.4.3 (concentration multiplied by the actual daily intake of the drug product of
2253 2.5 grams). The maximum daily intake given for each elemental impurity is not a
2254 summation of values found in the individual columns.

2255 This calculation also demonstrates that no elemental impurities exceed their PDEs. Thus
2256 if these concentrations in each component are not exceeded, the drug product is assured
2257 to meet the PDEs for each identified elemental impurity.

2258 The factor of 4 increase in Option 2a for permitted concentration seen when comparing
2259 Option 1 and Option 2a concentration limits is due to the use of 10 grams and 2.5 grams
2260 respectively as daily intake of the drug product.

2261

2262 **Table A.4.3: Calculation of Maximum Permitted Concentrations Assuming**
2263 **Uniform Concentrations in a Product with a Specified Daily Intake:**

Component	Maximum Permitted Concentration (µg/g)						
	Pb	As	Cd	Hg	Pd	V	Ni
Drug Substance	2	6	2	16	40	48	240
MCC	2	6	2	16	40	48	240
Lactose	2	6	2	16	40	48	240
Ca Phosphate	2	6	2	16	40	48	240
Crospovidone	2	6	2	16	40	48	240
Mg Stearate	2	6	2	16	40	48	240
HPMC	2	6	2	16	40	48	240
Titanium Dioxide	2	6	2	16	40	48	240
Iron Oxide	2	6	2	16	40	48	240
Maximum Daily intake, µg	**5.0**	**15**	**5.0**	**40**	**100**	**120**	**600**
PDE, µg/day	**5.0**	**15**	**5.0**	**40**	**100**	**120**	**600**

2264 **Option 2b:** Permitted concentration limits of elemental impurities across drug product
2265 component materials for a product with a specified daily intake:

2266 For this example, consider the same solid oral drug product with a maximum daily
2267 intake of 2.5 grams, containing 9 components (1 drug substance and 8 excipients, see
2268 Table A.4.1) used in Option 1 and 2a. The drug substance synthesis uses Pd and Ni
2269 catalysts, and the applicant is also concerned about Pb, As, Cd, Hg, and V on the basis of
2270 the risk assessment. To use Option 2b, the applicant must use the composition of the
2271 drug product and have additional knowledge regarding the content of each elemental
2272 impurity in the components. The applicant has generated the following data on
2273 elemental impurities in the components of the drug product:

2274 **Table A.4.4: Measured Concentrations of Elemental Impurities (µg/g) in the**
2275 **Components**

Component	Measured Concentration (µg/g)						
	Pb	As	Cd	Hg	Pd	V	Ni
Drug Substance	ND	0.5	ND	ND	20	ND	50
MCC	0.1	0.1	0.1	0.1	*	ND	ND
Lactose	0.1	0.1	0.1	0.1	*	ND	ND
Ca Phosphate	1	1	1	1	*	10	5
Crospovidone	0.1	0.1	0.1	0.1	*	ND	ND
Mg Stearate	0.5	0.5	0.5	0.5	*	ND	0.5
HPMC	0.1	0.1	0.1	0.1	*	ND	ND
Titanium Dioxide	20	1	1	1	*	1	ND
Iron Oxide	10	10	10	10	*	2000	50

2276 ND = Below the detection limit

2277 * = The risk assessment identified that Pd was not a potential elemental impurity; a quantitative
2278 result was not obtained.

2279 The applicant also knows the maximum daily intake of the drug product is 2.5 grams
2280 and determines the maximum daily intake for each component as shown in Table A.4.5.

2281 Based on the observed levels (see Table A.4.4), the applicant evaluated the potential
2282 maximum permitted concentrations of each elemental impurity in the components. The
2283 concentrations selected (see Table A.4.5) were set at levels that would ensure the PDE is
2284 met if the maximum permitted concentration was reached for each component. The
2285 maximum daily intake in Table A.4.5 is the summation of the values obtained by
2286 multiplying the actual weight of the component by the maximum permitted
2287 concentration for each elemental impurity across all components.

2288 **Table A.4.5: Maximum Permitted Concentrations of Elemental Impurities in the**
2289 **Components**

Component	Maximum Permitted Concentration (µg/g)						
	Pb	As	Cd	Hg	Pd	V	Ni
Drug Substance	**	5	**	**	500	**	2000
MCC	0.5	5	1	10	*	**	**
Lactose	0.5	5	1	10	*	**	**
Ca Phosphate	5	5	5	40	*	125	475
Crospovidone	0.5	5	1	10	*	**	**
Mg Stearate	5	10	5	100	*	**	50
HPMC	2.5	5	1	10	*	**	**
Titanium Dioxide	40	20	10	25	*	50	**
Iron Oxide	20	100	50	200	*	5000	2000
Maximum Daily intake, µg	**4.3**	**14.5**	**4.8**	**39.9**	**100**	**120**	**598**
PDE, µg/day	**5.0**	**15**	**5.0**	**40**	**100**	**120**	**600**

2290 * The risk assessment identified that Pd was not a potential elemental impurity; a quantitative
2291   result was not obtained.
2292 ** Quantitative results demonstrated less than the limit of detection.

2293 **Option 3:** Finished Product Analysis

2294 For this example, consider the same solid oral drug product with a maximum daily
2295 intake of 2.5 grams, containing 9 components (1 drug substance and 8 excipients) used in
2296 Option 1, 2a and 2b. The drug substance synthesis uses Pd and Ni catalysts, and the
2297 applicant is also concerned about Pb, As, Cd, Hg, and V on the basis of the risk
2298 assessment. The maximum concentration of each elemental impurity in the drug
2299 product may be calculated using the daily intake of drug product and the PDE of the
2300 elemental impurity using equation 1. The total mass of each elemental impurity should
2301 be not more than the PDE.

2302 $$Concentration(\mu g \, / \, g) = \frac{PDE(\mu g \, / \, day)}{2.5(g \, / \, day)}$$

2303 **Table A.4.6: Calculation of Concentrations for the Finished Product**

		Maximum Permitted Concentration (µg/g)						
	Daily Intake (g)	Pb	As	Cd	Hg	Pd	V	Ni
Drug Product	2.5	2	6	2	16	40	40	800
Maximum		5	15	5	40	100	120	600

Daily Intake (µg)							

2304 **Illustrative Example – Elemental Impurities Assessment**
2305 The following example is intended as illustration of an elemental impurities risk
2306 assessment. This example is intended for illustrative purposes and not as the only way
2307 to document the assessment.   There are many different ways to approach the risk
2308 assessment process and its documentation.

2309 This example relies on the oral drug product described in Appendix 4. Consider a solid
2310 oral drug product with a maximum daily intake of 2.5 grams, containing 9 components (1
2311 drug substance and 8 excipients). The drug substance synthesis uses Pd and Ni catalysts.

2312 The applicant conducts the risk assessment starting with the identification of potential
2313 elemental impurities following the process described in Section 5. Since the applicant
2314 had limited historical data for the excipients used in the drug product, the applicant
2315 determined that the Class 1 elementals (As, Cd, Hg, Pb) would be taken through the
2316 evaluation phase. The table below shows a summary of the findings of the identification
2317 stage of the assessment.

2318 **Table A.4.7: Identification of Potential Elemental Impurities**

	Potential Elemental Impurities			
Component	Intentionally added	Potential elemental impurities with a relatively high abundance and/or are impurities in excipients or reagents	Potential elemental impurities from manufacturing equipment	Potential elemental impurities from container closure systems
Drug Substance	Pd, Ni	As	Ni	None
MCC	None	As, Cd, Hg, Pb		None
Lactose	None	As, Cd, Hg, Pb		None
Ca Phosphate	None	As, Cd, Hg, Pb	V, Ni	None
Crospovidone	None	As, Cd, Hg, Pb		None
Mg stearate	None	As, Cd, Hg, Pb	Ni	None
HPMC	None	As, Cd, Hg, Pb		None
Titanium Dioxide	None	As, Cd, Hg, Pb	V	None
Iron Oxide	None	As, Cd, Hg, Pb	V, Ni	None

2319
2320 The identification phase of the assessment identified seven potential elemental
2321 impurities requiring additional evaluation. Three of the identified elemental impurities
2322 were found in multiple components. The applicant continued the risk assessment
2323 collecting information from the vendor and available development data. The summary of
2324 the results can be found in Table A.4.3. The application of the individual component data
2325 to the evaluation in the assessment process is shown below in Table A.4.8.
2326

2327 **Table A.4.8: Elemental Impurity Assessment – Evaluation of Daily Contribution to the Total Mass of Elemental Impurities in the Drug Product**

Component	Daily intake, g	Measured Concentration (µg/g)							Total Daily Mass of Elemental Impurity, µg						
		Pb	As	Cd	Hg	Pd	V	Ni	Pb	As	Cd	Hg	Pd	V	Ni
Drug Substance	0.2	ND	0.5	ND	ND	20	ND	50	0	0.1	0	0	4	0	10
MCC	1.1	0.1	0.1	0.1	0.1	*	ND	ND	0.11	0.11	0.11	0.11	0	0	0
Lactose	0.45	0.1	0.1	0.1	0.1	*	ND	ND	0.045	0.045	0.045	0.045	0	0	0
Ca Phosphate	0.35	1	1	1	1	*	10	5	0.35	0.35	0.35	0.35	0	3.5	1.75
Crospovidone	0.265	0.1	0.1	0.1	0.1	*	ND	ND	0.0265	0.0265	0.0265	0.0265	0	0	0
Mg stearate	0.035	0.5	0.5	0.5	0.5	*	ND	0.5	0.0175	0.0175	0.0175	0.0175	0	0	0.0175
HPMC	0.06	0.1	0.1	0.1	0.1	*	ND	ND	0.006	0.006	0.006	0.006	0	0	0
Titanium Dioxide	0.025	20	1	1	1	*	1	ND	0.5	0.025	0.025	0.025	0	0.025	0
Iron Oxide	0.015	10	10	10	10	*	400	50	0.15	0.15	0.15	0.15	0	6	0.75
						total daily mass, µg/day			1.2	0.8	0.7	0.7	4.0	9.5	12.5

2328

2329 **Table A.4.9: Assessment Example – Data Entry Descriptions**

2330 Column 1: Review the components of drug product for any elements intentionally added in the production (the primary source is the
2331 drug substance). For those used, record the elements for further consideration in the assessment.
2332 Column 2: Identify any potential elements or impurities that are associated with excipients or reagents used in the preparation of the
2333 drug product. Record the source(s) for further consideration in the assessment.
2334 Column 3: Identify any elemental impurities known or expected to be leached from the manufacturing equipment. Record the specific
2335 elemental impurities for further consideration in the assessment.
2336 Column 4: Identify any elemental impurities known or expected to be leached from the container closure system. Record the specific
2337 elemental impurities for further consideration in the assessment.
2338 Column 5: Calculate the total contribution of the potential elemental impurity by summing the contributions across the components
2339 of the drug product.

2340 Column 6: Assess the variability of the elemental impurity level(s) in the components
2341 Column 7: Enter the control threshold of each potential elemental impurity identified. If the variability is known and it is within
2342 acceptable limits, the control threshold (30% of the PDE) for each elemental impurity can be applied.
2343 Column 8: Describe action taken – none if the value in column 6 is less than or equal to the control threshold (column 7). Define
2344 control element if material variability is high or control threshold is exceeded.
2345

	1	2	3	4	5	6	7	8
Element	Intentionally added (if used in the process)	Elemental impurities with a relatively high abundance and/or are impurities in excipients or reagents	Manufacturing equipment	Leached from container closure systems	Total elemental impurity contribution µg/day	Acceptable variability of elemental impurity contribution	Control threshold	Action
As	No	Observed contaminant in all excipients and drug substance	No	No	0.8	yes	4.5	no further controls required
Cd	No	Observed contaminant in all excipients	No	No	0.7	yes	1.5	no further controls required
Hg	No	Observed contaminant in all excipients	No	No	0.7	yes	12	no further controls required
Pb	No	Observed contaminant in all excipients	No	No	1.2	yes	1.5	no further controls required
Pd	API catalyst	No	No	No	4.0	yes	30	no further controls required
Ni	API catalyst	Observed in 3 excipients	No	No	12.5	yes	180	no further controls required
V	No	Observed in 3 excipients	No	No	9.5	yes	36	no further controls required

2346